EXHIBIT 33

Chromium Hexavalent Compounds

CAS No. 18540-29-9

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Chromium hexavalent (VI) compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Epidemiological studies in various geographical locations have consistently reported increased risks of lung cancer among workers engaged in chromate production, chromate pigment production, and chromium plating. Epidemiological studies of lung cancer among ferrochromium workers were inconclusive. Exposure to specific chromium compounds varies by industry. Chromate-production workers are exposed to a variety of chromium compounds, including hexavalent (VI) and trivalent (III) compounds. Chromate-pigment workers are exposed to chromates in the pigment and to soluble chromium(VI) compounds used in pigment production. Chrome platers are exposed to soluble chromium(VI) compounds and possibly to nickel. Ferrochromium workers are exposed mainly to chromium(III) compounds and possibly to chromium(VI) compounds. Epidemiological studies of stainless-steel welders exposed to chromium(VI) compounds also found an increased risk of lung cancer; however, these studies are of limited use for evaluation of chromium's carcinogenicity, because the welders were also exposed to other potential carcinogens. In addition, epidemiological studies of chromate production workers, chromate pigment workers, and chrome platers found an increased risk of a rare cancer of the sinonasal cavity. The data for cancer at sites other than the lung and sinonasal cavity were unclear. The International Agency for Research on Cancer concluded that there was sufficient evidence in humans for the carcinogenicity of chromium(VI) compounds as encountered in the chromate-production, chromate-pigment-production, and chromium-plating industries (IARC 1973, 1979, 1990).

Cancer Studies in Experimental Animals

Exposure to chromium(VI) compounds (calcium chromate, chromium trioxide, or sodium dichromate) via inhalation or intratracheal or intrabronchial implantation caused benign and/or malignant lung tumors in rats and/or mice. Intrabronchial implantation of zinc chromate or strontium chromate also caused bronchial tumors in rats, and inhalation exposure to chromium trioxide caused benign nasal tumors in mice. In addition, cancer at the injection site was observed in rats following administration of chromium compounds (calcium chromate, lead chromate, basic lead chromate, zinc chromate, or strontium chromate) by intrapleural, subcutaneous, or intramuscular injection and in mice following intramuscular injection of calcium chromate (IARC 1980, 1990). IARC (1990) concluded that there was sufficient evidence in experimental animals for the carcinogenicity of calcium chromate, lead chromates, strontium chromate, and zinc chromates and limited evidence for the carcinogenicity of chromium trioxide and sodium dichromate.

Since chromium hexavalent compounds were reviewed for listing in the *First Annual Report on Carcinogens* and reviewed by IARC in 1990, the National Toxicology Program has conducted two-year cancer studies of sodium dichromate in rats and mice. Sodium dichromate administered in the drinking water caused cancer of the oral cavity (squamous-cell carcinoma of the oral mucosa) in rats and increased the combined incidence of benign and malignant tumors (adenoma and carcinoma) of the small intestine (duodenum, jejunum, or ileum) in mice (NTP 2008).

Studies on Mechanisms of Carcinogenesis

Chromosomal aberrations, sister chromatid exchange, and aneuploidy were observed in workers exposed to chromium(VI) compounds. Chromium(VI) compounds also caused genetic damage in a variety of test systems. Most caused mutations and DNA damage in bacteria; however, the poorly soluble compounds had to be dissolved in acids or alkalis to produce genetic effects. A few compounds also caused mutations in yeast and insects. Many chromium(VI) compounds caused genetic damage in cultured human and other animal cells and in experimental animals exposed *in vivo*. The compounds tested included ammonium chromate and dichromate, calcium chromate, chromium trioxide, sodium chromate and dichromate, potassium chromate and dichromate, strontium chromate, and the industrial product basic zinc chromate (zinc yellow). Among the types of genetic damage observed were gene mutations (including dominant lethal mutations), DNA damage, sister chromatid exchange, chromosomal aberrations, and cell transformation (IARC 1990).

IARC (1990) concluded that there was sufficient evidence in humans for the carcinogenicity of chromium(VI) compounds based on the combined results of epidemiological studies, cancer studies in experimental animals, and evidence that chromium(VI) ions generated at critical sites in the target cells were responsible for the carcinogenic action observed.

Properties

Elemental chromium is a transition-group metal belonging to group VIB of the periodic table and has oxidation states ranging from −2 to +6, of which the divalent (+2, II), trivalent (+3, III), and hexavalent (+6, VI) forms are the most important. Elemental chromium does not occur naturally in the environment. The divalent (chromous) state is readily oxidized to the more stable trivalent (chromic) state. Although the hexavalent state (including chromates) is more stable than the divalent state, it is rarely found in nature. Chromium(VI) compounds are strong oxidizing agents and are highly corrosive. In the environment, they generally are reduced to chromium(III) compounds. The chromium(VI) compounds most commonly encountered in industry are calcium chromate, chromium trioxide, sodium chromate and dichromate, potassium chromate and dichromate, lead chromate, strontium chromate, and zinc chromate (IARC 1990, Costa 1997). However, this listing applies to all hexavalent chromium compounds, not just to those specified above.

Calcium chromate occurs as yellow crystals or a bright-yellow powder. It is slightly soluble in water and soluble in dilute acids, and it reacts with acids and ethanol. Although calcium chromate is not flammable, toxic chromium fumes may be formed in fires, and mixtures with boron burn violently when ignited. Chromium trioxide (also known as chromic trioxide) occurs as dark-red or brown crystals, flakes, or granular powder and is soluble in water, ethyl alcohol, ethyl ether, sulfuric acid, and nitric acid. Contact of chromium trioxide with organic chemicals may result in violent or explosive reactions, and fires with chromium trioxide may produce irritating, corrosive, and toxic gases (ATSDR 2000, HSDB 2009). Lead chromate occurs as yellow, orange, or red crystals or a yellow or orange-yellow powder that is insoluble in water, acetic acid, and ammonia but soluble in dilute nitric acid. When heated, it emits highly toxic fumes, and it may react explosively with azo dyes. The term "lead chromate" is also used to refer to various commercial lead chromate pigments (IARC

1980, 1990, HSDB 2009). Potassium chromate occurs as yellow crystals and is soluble in water but insoluble in ethanol. Potassium dichromate occurs as red or orange-red crystals and is soluble in water but insoluble in ethanol and acetone. It poses a dangerous fire risk when in contact with organic materials or finely divided combustible materials, such as sawdust (ATSDR 2000, HSDB 2009).

Sodium chromate occurs as yellow crystals and is soluble in water and slightly soluble in methanol. Although it is not flammable, toxic chromium oxide fumes may be formed in fires with sodium chromate (ATSDR 2000, HSDB 2009). Sodium dichromate occurs as bright orange-red or red hygroscopic crystals and is soluble in water and methanol. It reacts explosively with hydrazine, acetic anhydride, boron, silicon, and other materials (IARC 1980, HSDB 2009). Strontium chromate occurs as yellow monoclinic crystals or a yellow powder. It is slightly soluble in water and soluble in dilute hydrochloric acid, nitric acid, and acetic acid. It is not flammable but reacts explosively with hydrazine (HSDB 2009). Zinc chromate occurs as lemon-yellow crystals or powder. It is insoluble in cold water and acetone, sparingly soluble in hot water, and soluble in acid and liquid ammonia. Zinc chromate reacts explosively with hydrazine. The term "zinc chromate" is also used to refer to various commercial zinc and zinc potassium chromates (IARC 1990, HSDB 2009). Physical and chemical properties of these chromium(VI) compounds are listed in the table below, along with their chemical formulas.

Use

The steel industry is the major consumer of chromium. In 2007, estimated consumption of chromium in the United States by end use was 78% in stainless and heat-resisting steel, 13.8% for other steel uses, 3.7% in superalloys, and 4.5% in other alloys and end uses (Papp 2009). Alloys of stainless steel and chromium typically contain between 11.5% and 30% chromium (ATSDR 2000). Chromium(VI) compounds are widely used as corrosion inhibitors, in the manufacture of pigments, in metal finishing and chrome plating, in stainless steel production, in leather tanning, and in wood preservatives (Costa 1997, ATSDR 2000). In 1996, about 52% of all chromium compounds used in the U.S. chemical industry were used in production of wood preservatives; the rest were used in leather tanning (13%), metals finishing (13%), pigments (12%), refractories (linings for high-temperature industrial furnaces) (3%), and other uses (7%) (ATSDR 2000). The use of chromium(VI) compounds in wood preservatives increased dramatically from the late 1970s to the early 2000s; however, this use is expected to decrease because of a voluntary phase-out of all residential uses of wood treated with chromated copper arsenate (pressure-treated wood) that went into effect December 31, 2003 (Brooks 2009). Chromium(VI) compounds are also used in textile-dyeing processes, printing inks, drilling muds, pyrotechnics, water treatment, and chemical synthesis (HSDB 2009).

Calcium chromate is used primarily as a corrosion inhibitor and as a depolarizer in batteries (IARC 1973, 1990, HSDB 2009). Chromium trioxide is used primarily in chrome plating and other metal finishing (particularly in the production of automobiles and military aircraft), in production of wood preservatives, as a corrosion inhibitor, and in production of organic chemicals and catalysts. Lead chromate has been used in paints and printing inks and as a colorant in vinyl, rubber, and paper. Potassium chromate is used in production of dyes and in textile-dyeing processes. Potassium dichromate has largely been replaced by sodium dichromate in many applications; however, it is still used in photomechanical processes and production of pigments and wood preservatives. Sodium chromate is used as a corrosion inhibitor and in textile dyeing processes, inks, paints, leather tanning, wood preservatives, drilling muds, cutting oils, water treatment, and production of other chromium compounds. Sodium dichromate is the primary base material for the production of chromium compounds and is used as a corrosion inhibitor, in metal treatments, in drilling muds, and in the production of dyes, wood preservatives, synthetic organic chemicals, and catalysts. Strontium chromate is used as a corrosion inhibitor and metal conditioner, in aluminum flake coatings, as a colorant in polyvinyl chloride, in pyrotechnics, in chrome plating, and for sulfate ion control in electrochemical processes. Zinc chromates are used as corrosion inhibitors and metal conditioners and in paints, varnishes, and oil colors.

Production

The United States is one of the world's leading producers of chromium compounds. U.S. primary production levels of chromium (i.e., mine production of chromite ore) have not been reported since 1961 (Papp 2007). One surface mine was developed in the United States in the mid to late 2000s (Papp 2009, USGS 2010), but production levels from that mine were not reported. Other domestic sources of chromium include recycled stainless-steel scrap, industry stocks, and the Defense National Stockpile. Overall U.S. production of chromium metal decreased between 2000 and 2008 (Papp 2009, USGS 2010), but production in 2015 (shown in the table on the next page) was similar to that in 2000. Apparent chromium consumption in 2017 (about 1.2 billion pounds) also was similar to that in 2000. In contrast, U.S. imports and exports of chromium metal were lower in 2017 than in 2000 (when they each totaled about 1 billion pounds) (USGS 2005, 2019).

The table also shows the production, import, and export data available for specific hexavalent chromium compounds. The United States has produced or imported several chromium compounds in quantities of at least 1 million pounds for decades, and some compounds have also been exported in large quantities. Production of sodium chromate and dichromate combined was about 280 million pounds in the late 1990s (HSDB 2009), similar to the figure reported in 2015 for production plus imports of sodium dichromate. In contrast, chromium trioxide production increased from around 66 million pounds in the late 1970s through the 1980s (IARC 1990, HSDB 2009) to over 100 million pounds in 2015. U.S. production of potassium chromate

Compound	Formula	Molec. wt.	Density (g/cm^3)[a]	Melting pt.	Dec.
Calcium chromate	$CaCrO_4$	156.1	2.89	NR	NR
Chromium trioxide	CrO_3	100.0	2.70	197°C	yes
Lead chromate	$PbCrO_4$	323.2	6.12	844°C	yes
Potassium chromate	K_2CrO_4	194.2	2.73	975°C	NR
Potassium dichromate	$K_2Cr_2O_7$	294.2	2.68	398°C	~500°C
Sodium chromate	Na_2CrO_4	162.0	2.72	792°C	NR
Sodium dichromate	$NaCr_2O_7$	262.0	2.52	357°C	400°C
Strontium chromate	$SrCrO_4$	203.6	3.90	NR	NR
Zinc chromate	$ZnCrO_4$	181.4	3.40	NR	NR

Source: HSDB 2009. [a]Source specifies the temperature at which density was determined for some but not all of the compounds. Dec. = decomposes; NR = not reported.

Chromium category	Quantity (lb)		
	Production (2015)	Imports (2017)	Exports (2017)
Metal (excluding alloys)	1 billion to 5 billion	32.0 million[a]	1.4 million[a]
Hexavalent compounds			
Chromium trioxide	100 million to 250 million	8.0 million	–
Potassium dichromate	–	66,313	4.7 million
Sodium dichromate	100 million to 250 million	200,984	–
Strontium chromate	1 million to 10 million	–	–

Sources: EPA 2016 (production volume = production + imports), USITC 2018 (imports and exports).
– = no data found.
[a]The reported value is for the sum of the following chromium metal categories: unwrought chromium (powders), chromium waste and scrap, and chromium and articles thereof, not elsewhere specified or included.

and dichromate combined or separately and of strontium chromate was generally less than 10 million pounds in the 1960s to 1970s (IARC 1990, HSBB 2009) and remained below 10 million pounds in 2015.

Chromium compounds that have been imported in quantities of at least 1 million pounds since the 1970s include sodium chromate and dichromate (over 40 million pounds in 2002 and 2008), chromium trioxide (over 35 million pounds in 2002), and potassium chromate and dichromate (about 1 to 2 million pounds in the mid 1980s) (IARC 1990, HSDB 2009), but only chromium trioxide imports exceeded 1 million pounds in 2017.

U.S. exports of sodium chromate and dichromate exceeded 50 million pounds in 1999, but no export data specific for either of these compounds were reported in 2017 (HSDB 2009, USITC 2018). U.S. exports of chromium trioxide were less than 10 million pounds in 1977, but approached 40 million pounds by 2008 (HSDB 2009, USITC 2009); however, no export data specific for chromium trioxide were reported in 2017. U.S. exports of potassium dichromate were only 170,000 lb in 2008 (USITC 2009), but approached 5 million pounds in 2017 (as shown in the table above).

Exposure

Chromium, in the form of unidentified chromium compounds, occurs naturally in the earth's crust and is widely distributed in air, water, soil, and food. Chromium(III) is an essential trace element in humans. The general population is exposed to some chromium(VI) compounds, but the levels of exposure vary. Environmental exposure specifically to chromium(VI) compounds is difficult to quantify, because specific forms of chromium seldom are identified in exposure studies. Although chromium(VI) compounds in the environment may be reduced to chromium(III) compounds, hexavalent forms can persist under some conditions. The general population may be exposed to chromium(VI) compounds through inhalation of ambient air, ingestion of water, or dermal contact with products that contain chromium(VI) compounds, such as pressure-treated wood. People who live near industrial facilities that use chromium(VI) compounds or near chromium waste disposal sites have the greatest potential for exposure (ATSDR 2000).

A 1990 study reported the average concentration of chromium(VI) to be 0.0012 μg/m^3 (range = < 0.001 to 3 μg/m^3) in indoor air samples collected from residences in Hudson County, New Jersey. Other reports of exposure to chromium were not specific for chromium(VI) compounds, but provide general information on exposure to chromium and chromium compounds. Between 1977 and 1984, typical total chromium concentrations in ambient air in the United States were less than 0.01 μg/m^3 in rural areas and 0.01 to 0.03 μg/m^3 in urban areas. Average atmospheric concentrations of chromium from more than 2,100 monitoring stations ranged from 0.005 to 0.525 μg/m^3. A survey of more than 3,800 tap water samples in 1974 and 1975 found chromium concentrations ranging from 0.4 to 8.0 μg/L, with a mean of 1.8 μg/L. In surveys of U.S. surface waters, chromium concentrations in rivers ranged from less than 1 to 30 μg/L, and concentrations in lakes typically were less than 5 μg/L. Typical chromium levels in most fresh foods are low; chromium was detected in vegetables, fruits, grains, cereals, eggs, meat, and fish at concentrations of between 20 and 520 μg/kg. The mean daily dietary intake of chromium was estimated to be less than 0.2 to 0.4 μg from air, 2.0 μg from water, and 60 μg from food (ATSDR 2000).

Evidence that people in the United States are exposed to some form of chromium is provided by the National Health and Nutrition Examination Survey for 2015–2016, which found that the 95th-percentile concentration of chromium in whole blood for the U.S. general population was 1.08 μg/L, based on samples from 3,442 individuals of all ages, both genders, and all race and ethnicity groups (CDC 2018).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of chromium compounds since reporting began in 1988 were lowest in 2001 (about half the average from 1988 to 2000). In 2007, 1,384 facilities released 12 million pounds of chromium, and 1,147 facilities released 51 million pounds of chromium compounds. The 100 facilities with the largest releases accounted for most of the total amounts released (TRI 2008).

Most occupational exposure to chromium(VI) compounds is through inhalation or dermal contact. Exposure to specific chromium compounds varies by industry. Chromate production workers are exposed to a variety of chromium compounds, including chromium(VI) and chromium(III) compounds. Chromate pigment workers are exposed to chromates in the pigment and to soluble chromium(VI) compounds used in pigment production. Chrome platers are exposed to soluble chromium(VI) compounds and possibly to nickel. Ferrochromium workers are exposed mainly to chromium(III) compounds and possibly to chromium(VI) compounds.

Occupational exposure to chromium generally exceeds nonoccupational exposure. However, concentrations of airborne chromium in workplaces have declined significantly since the 1980s because of improved emission controls. Typical concentration ranges for airborne chromium(VI) in industries that use chromium(VI) compounds are as follows: stainless-steel welding, 50 to 400 μg/m^3; chromate production, 100 to 500 μg/m^3; chrome plating, 5 to 25 μg/m^3; ferrochrome alloy production, 10 to 140 μg/m^3; and chromate pigment production, 60 to 600 μg/m^3 (IARC 1990, ATSDR 2000). In the tanning industry, hides are soaked with chromium(VI) compounds in the presence of other chemicals that reduce them to chromium(III) compounds (Costa 1997); therefore, exposure in the tanning industry is almost exclusively to soluble chromium(III) (ATSDR 2000). In a study assessing chromium exposure among stainless-steel welders and mild-steel welders, chromium levels in blood, plasma, and urine were higher among the stainless-steel welders, particularly those engaged in manual metal arc welding, which produces fumes with high concentrations of total water-soluble chromium, mainly chromium(VI) (which constituted up to 61% of total soluble chromium) (Edme *et al.* 1997).

The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 16,576 workers potentially were exposed to chromium (types and compounds not specified), 42,043 to potassium dichromate, and 3,519 to calcium chromate (NIOSH 1976). The National Occupational Exposure Survey (conducted 1981 to 1983) estimated that 386,142 workers, including 10,433 women, potentially were exposed to chromium; 61,073, including 19,198 women, to potassium dichromate; 32,129, including 5,565 women, to cal-

cium chromate; and 30,784, including 8,856 women, to lead chromate (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Chromium hexavalent compounds are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Chromium compounds are listed as mobile source air toxics for which regulations are to be developed.

National Emission Standards for Hazardous Air Pollutants: Chromium compounds are listed as hazardous air pollutants.

Urban Air Toxics Strategy: Chromium compounds have been identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Numerous hexavalent chromium compounds are designated as hazardous substances.

Effluent Guidelines: Chromium and chromium compounds are listed as toxic pollutants.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 5,000 lb for chromium; = 10 lb for chromic acid, sodium chromate, ammonium chromate, potassium chromate, strontium chromate, calcium chromate, lithium chromate, potassium bichromate, ammonium bichromate, sodium bichromate; = 1,000 lb for chromic acetate, chromic sulfate.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Chromium compounds are listed substances subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

Wood intended to be used in residential settings cannot be treated with chromated copper arsenate.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 5.0 mg/L for chromium.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of chromium hexavalent compounds = F006, F019, K002, K003, K004, K005, K006, K007, K008, K048, K049, K050, K051, K061, K062, K069, K086, K100; on the presence of chromium = F032, F034, F035, F037, F038.

Chromium compounds are listed as hazardous constituents of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.1 mg/L for total chromium.

Food and Drug Administration (FDA, an HHS agency)

Maximum permissible level of chromium in bottled water = 0.1 mg/L.

Specified color additives may contain chromium (as chromates) under certain restrictions.

Specified color additives may contain chromium at levels no greater than 50 ppm.

Hydrolyzed leather meal used in the feed of animals may contain chromium at levels not to exceed 2.75% of the total by weight; finished feeds may not contain more than 1% hydrolyzed leather meal by weight.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2018, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.005 mg/m^3 for hexavalent chromium and compounds; = 0.1 mg/m^3 where the limit of 0.005 mg/m^3 has been stayed or otherwise is not in effect.

Comprehensive standards have been developed for occupational exposure to hexavalent chromium in any form and in any compound.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.0002 mg/m^3 for water-soluble chromium(VI) compounds; = 0.01 mg/m^3 for insoluble chromium(VI) compounds.

Threshold limit value – short-term exposure limit (TLV-STEL) = 0.0005 mg/m^3 for water-soluble chromium(VI) compounds.

Biological exposure index (BEI) (end of shift at end of workweek) = 25 µg/L for total chromium in urine; (increase during shift) = 10 µg/L for for total chromium in urine.

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Immediately dangerous to life and health (IDLH) limit = 15 mg/m^3 as hexavalent chromium for chromic acid and chromates.

Recommended exposure limit (REL) (time-weighted-average workday) (8-h TWA) = 0.0002 mg/m^3 (as hexavalent chromium).

NIOSH considers all hexavalent chromium compounds to be potential occupational carcinogens (based on listings for chromic acid and chromates and for chromyl chloride).

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Nickel Compounds and Metallic Nickel

Introduction

Nickel compounds and metallic nickel have many industrial and commercial applications, including use in stainless steel and other nickel alloys, catalysts, batteries, pigments, and ceramics. Nickel and Certain Nickel Compounds were listed in the *First Annual Report on Carcinogens* (1980) as *reasonably anticipated to be human carcinogens.* Nickel compounds as a class were first listed as *known to be human carcinogens* in the *Tenth Report on Carcinogens* (2002); this listing supersedes the listing of "certain nickel compounds" and applies to all members of the class. Metallic nickel was reevaluated in 2000 and remains listed as *reasonably anticipated to be a human carcinogen.* Nickel alloys were reviewed in 2000 but were not recommended for listing in the Report on Carcinogens (see Appendix C).

The profiles for nickel compounds and metallic nickel follow this introduction. The evidence for carcinogenicity from cancer studies in experimental animals and humans is discussed separately for nickel compounds and metallic nickel. However, most of the information on mechanisms of carcinogenesis, properties, use, production, exposure, and regulations is common to both nickel compounds and metallic nickel and therefore is combined into one section following the discussions of cancer studies.

Nickel Compounds

No separate CAS No. assigned for nickel compounds as a class

Known to be human carcinogens

First listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

Nickel compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic studies. The combined results of epidemiological studies, mechanistic studies, and cancer studies in rodents support the concept that nickel compounds generate nickel ions in target cells at sites critical for carcinogenesis, thus allowing consideration and evaluation of these compounds as a single group.

Cancer Studies in Humans

Several epidemiological cohort studies of workers exposed to various nickel compounds showed an elevated risk of death from lung cancer and nasal cancer. Although the precise nickel compound responsible for the carcinogenic effects in humans is not always clear, studies indicate that nickel sulfate and the combinations of nickel sulfides and oxides encountered in the nickel-refining industry cause cancer in humans. The International Agency for Research on Cancer concluded that there was sufficient evidence of the carcinogenicity of nickel compounds encountered in the nickel-refining industry in humans (IARC 1990). In an additional study, nickel-refinery workers exposed primarily to soluble nickel compounds had a significant excess risk of lung cancer, and smoking and nickel exposure had a synergistic effect on cancer risk (Anderson *et al*. 1996). These workers also had an excess risk of nasal cancer.

Cancer Studies in Experimental Animals

In rats and in some studies with mice, inhalation or intratracheal instillation of nickel subsulfide or nickel oxide led to dose-related induction of benign and malignant lung tumors, including carcinoma (IARC 1990, NTP 1996a,b). Inhalation of nickel compounds also caused tumors at tissue sites other than the lung; in particular, benign or malignant adrenal-gland tumors (pheochromocytoma) were observed in rats (NTP 1996a,b). Injection of rodents with various nickel compounds was repeatedly shown to cause dose-dependent increases in tumors in several species and at several different sites. Subcutaneous, intramuscular, intraperitoneal, subperiosteal, intrafemoral, intrapleural, intracerebral, intrarenal, intratesticular, and intraocular injections of nickel compounds all caused cancer (usually sarcoma) at the injection site. Injection of nickel also produced distant tumors of the liver in some strains of mice. IARC concluded that there was sufficient evidence of the carcinogenicity of several nickel compounds (monoxides, hydroxides, and crystalline sulfides) in experimental animals (IARC 1990).

Soluble nickel acetate is a complete transplacental carcinogen in rats. Brief exposure of pregnant rats to nickel acetate by intraperitoneal injection during pregnancy caused pituitary cancer in the offspring. Transplacental exposure to nickel acetate followed by exposure of the offspring to barbital (a known tumor promoter) caused kidney tumors (renal cortical and pelvic tumors) (Diwan *et al.* 1992). In adult rats, injection of soluble nickel salts followed by barbital exposure caused kidney cancer (renal cortical adenocarcinoma) that frequently metastasized to the lung, liver, and spleen (Kasprzak *et al.* 1990).

Metallic Nickel

CAS No. 7440-02-0

Reasonably anticipated to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as Ni

Carcinogenicity

Metallic nickel is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Metallic nickel caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. In both rats and hamsters, metallic nickel powder caused tumors when administered by intratracheal instillation or by subcutaneous, intramuscular, or intraperitoneal injection. Intratracheal instillation of metallic nickel powder primarily caused adenocarcinoma, whereas injection most frequently caused sarcoma, demonstrating that metallic nickel can induce both epithelial and connective-tissue tumors (IARC 1973, 1976, 1990).

Cancer Studies in Humans

The available epidemiological studies of workers exposed to metallic nickel are limited by inadequate exposure information, low exposure levels, short follow-up periods, and small numbers of cases.

Nickel Compounds and Metallic Nickel

Studies on Mechanisms of Carcinogenesis

The available evidence suggests that metallic nickel has carcinogenic properties because it can slowly dissolve in the body and release ionic nickel, an active genotoxic and carcinogenic form of nickel. There is no evidence to suggest that the mechanisms by which nickel causes tumors in experimental animals would not also operate in humans.

Many studies in cultured rodent and human cells have shown that a variety of nickel compounds, including both soluble and insoluble forms of nickel, caused genetic damage, including DNA strand breaks, mutations, chromosomal damage, cell transformation, and disrupted DNA repair. Chromosomal aberrations have been observed in humans occupationally exposed to nickel. Nickel can bind ionically to cellular components, including DNA. The reduction-oxidation activity of the nickel ion may produce reactive oxygen species that attack DNA, and exposure to nickel ion *in vitro* or *in vivo* can result in production of 8-hydroxy-2′-deoxyguanosine in target tissues for cancer caused by nickel (IARC 1990, Kasprzak *et al*. 1990).

The carcinogenic potency of various nickel compounds varies widely, based on solubility properties and speciation. Studies indicate that soluble nickel salts can be complete carcinogens (Diwan *et al.* 1992) or initiators of carcinogenesis (Kasprzak *et al*. 1990) at tissue sites distant from the site of administration, which confirms that ionic nickel is the carcinogenic species. Differences in the potency of nickel compounds may relate to the specific properties of the compounds that affect the availability of ionic nickel at target sites. The listings of nickel compounds and metallic nickel are based on a large body of scientific evidence supporting the concept that nickel ion is carcinogenic. The hazard associated with a particular nickel compound is related largely to the compound's propensity to release ionic nickel in the body. The evidence suggests that the relatively insoluble metallic nickel is less likely to present a carcinogenic hazard than are the nickel compounds that tend to release proportionately more nickel ion. This view agrees with that expressed by IARC (1990), which based its evaluation of the carcinogenicity of nickel compounds as a group on the combined results of human epidemiological studies, cancer studies in experimental animals, and other data supporting the "underlying concept that nickel compounds can generate nickel ions at critical sites in their target cells." The IARC review noted that the carcinogenicity of nickel compounds depends not solely on their capacity to release ionic nickel, but also on factors that promote localization of high concentrations of nickel ions at critical tissue sites. This conclusion is consistent with evidence from studies in experimental animals indicating that nickel compounds of moderate solubility can, under certain exposure conditions, be more carcinogenic than more soluble compounds. Therefore, it is difficult to predict with any certainty the relative carcinogenic hazard posed by a particular nickel compound without a full understanding of its ability to release ionic nickel under specific exposure conditions.

Properties

Metallic nickel is a group 10 metallic element. It is a lustrous, silvery, hard ferromagnetic metal or a gray powder. It has a vapor pressure of 1 mm Hg at 1,810°C. Metallic nickel is insoluble in water and ammonia, slightly soluble in hydrochloric acid and sulfuric acid, and soluble in dilute nitric acid. It is resistant to attack by air and water at standard temperatures. However, powdered nickel is reactive in air and may ignite spontaneously (IARC 1990, ATSDR 1997, HSDB 2009).

Nickel oxides and hydroxides are practically insoluble in water and soluble in acids and ammonium hydroxide. Nickel monoxide (also known as nickel oxide) is a green to black powder that becomes yellow when heated. The temperature at which the crystal is formed determines the color of the crystal. It is soluble in acids and ammonium hydroxide. Nickel monoxide reacts with acids to form nickel salts and soaps, and mixtures of nickel monoxide and barium oxide react violently with iodine and hydrogen sulfide in air. Nickel hydroxide occurs either as green crystals or as a black powder. It does not burn, but it may produce toxic gases when heated to decomposition. It is available at 97% purity (IARC 1990, HSDB 2009).

Nickel sulfides are insoluble in water, and some occur in more than one form. Nickel subsulfide (α form) occurs as lustrous pale-yellowish or bronze crystals that are soluble in nitric acid. Nickel sulfide occurs in three forms (α, β, and amorphous) as dark-green to black crystals or powder. Nickel disulfide occurs as black crystals or powder and decomposes at temperatures above 400°C (IARC 1990).

Nickel salts are green to yellow crystals that generally are soluble in water and decompose when heated. Nickel acetate occurs as a dull-green powder that effloresces somewhat in air. It is available as the tetrahydrate at greater than 97% purity. Nickel chloride occurs as yellow (anhydrous) or green (hexahydrate) deliquescent crystals. It is soluble in ethanol and ammonium hydroxide and insoluble in ammonia. The hexahydrate form is available as a laboratory reagent at greater than 99% purity or as industrial products containing approximately 24.7% nickel. Nickel sulfate occurs as yellow, green, or blue crystals and is available in anhydrous, hexahydrate, or heptahydrate forms. The hexahydrate melts at 53.3°C and the heptahydrate at 99°C; both forms are available at greater than 99% purity. Nickel carbonate occurs as light-green rhombic crystals. It is practically insoluble in water but soluble in dilute acids and ammonia. Laboratory reagent grades contain 45% or 47.5% nickel, and industrial grades contain approximately 45% nickel (IARC 1990, HSDB 2009).

Nickel carbonyl occurs as a colorless, volatile, highly flammable liquid with a musty odor. It is practically insoluble in water but soluble in alcohol, benzene, chloroform, acetone, and carbon tetrachloride, and insoluble in dilute acids and dilute alkalis. It is available in a technical grade at greater than 99% purity. Nickel carbonyl decays spontaneously in air and may decompose violently when exposed to heat or flame in the presence of air or oxygen. When heated or on contact with acid or acid fumes, it emits toxic carbon monoxide fumes (HSDB 2009). Nickelocene occurs as dark-green crystals. It is insoluble in water but soluble in common organic solvents. It is highly reactive and decomposes in air, acetone, alcohol, and ether. It is available in solid form at greater than 90% purity or as an 8% to 10% solution in toluene (IARC 1990).

Physical and chemical properties of metallic nickel and selected nickel compounds are listed in the table on the next page, along with their chemical formulas.

Use

Because of its unique properties, nickel has many uses in industry. The majority (about 80%) of all nickel is used in alloys, because it imparts such properties as corrosion resistance, heat resistance, hardness, and strength (ATSDR 1997). The main uses of nickel are in the production of stainless steel, copper-nickel alloys, and other corrosion-resistant alloys. Pure nickel metal is used in electroplating, as a chemical catalyst, and in the manufacture of alkaline batteries, coins, welding products, magnets, electrical contacts and electrodes, spark plugs, machinery parts, and surgical and dental prostheses (IARC 1990, HSDB 2009). In 2009, 45% of the nickel used in the United States was used in stainless and alloy steel production, 39% in nonferrous alloys and superalloys, 11% in electroplating, and 5% in other uses. The end uses in 2009 were 32% in transportation, 14% in the chemical industry, 10% in electrical equipment, 8% in construction, 8% in fabricated metal products, 8% in the petroleum industry, 6% in household appliances, 6% in machinery, and 8% for other uses (Kuck 2010).

Nickel oxide sinters (a coarse form of nickel monoxide) are used in steel and alloy manufacturing. Green nickel monoxide is used in electronics, in fuel-cell electrodes, as a colorant in ceramics and glass, and to make nickel catalysts. Black nickel monoxide is used in the ceramics industry, to manufacture nickel catalysts, and to manufacture nickel salts. Nickel hydroxide is used in nickel-cadmium batter-

Substance	Formula	Atomic or molec. wt.	Specific gravity	Melting point	Boiling point
Metallic nickel	Ni	58.7	8.91	1,455°C	2,730°C
Nickel monoxide	NiO	74.7	6.72	1,955°C	NR
Nickel hydroxide	$Ni(OH)_2$	92.7	4.1	230°C (dec)	N/A
Nickel acetate	$Ni(C_2H_3O_2)_2$	176.8	1.80	NR	16.6°C
Nickel chloride	$NiCl_2$	129.6	3.51	1,001°C	973°C (sub)
Nickel sulfate	$NiSO_4$	154.8	4.01	848°C (dec)	N/A
Nickel carbonate	$NiCO_3$	118.7	4.39	dec	N/A
Nickel carbonyl	$Ni(CO)_4$	170.7	1.32	–19°C	43°C

Source: HSDB 2009. NR = not reported; dec = decomposes; N/A = not applicable; sub = sublimes.

ies and as a catalyst intermediate. Nickel sulfides are used as catalysts in the petrochemical industry when high concentrations of sulfur are present in the distillates and as intermediates in hydrometallurgical processing of silicate-oxide nickel ores (IARC 1990). Nickel subsulfide is used in lithium batteries (HSDB 2009).

Nickel salts are widely used in industry. Nickel acetate is used as a catalyst intermediate, as a dye fixative in the textile industry, in electroplating, and as a sealer for anodized aluminum. Nickel chloride is used in nickel catalysts, to absorb ammonia in industrial gas masks, and in electroplating. Nickel sulfates are used in electroplating and electrodeless nickel plating, as chemical intermediates to produce other nickel compounds, and in nickel flashings on steel to prepare it to be porcelain-enameled. Nickel carbonate is used to prepare nickel monoxide, nickel powder, nickel catalysts, colored glass, and certain nickel pigments. It also is used in electroplating and as a catalyst to remove organic contaminants from water (IARC 1990, HSDB 2009).

Nickel carbonyl is used in the production of high-purity nickel powder by the Mond process and for continuous nickel coatings on steel and other metals. It also has many small-scale applications, such as vapor plating of nickel and deposition of nickel in semiconductor manufacturing. Nickelocene is used as a catalyst and complexing agent (IARC 1990).

Production

Nickel is refined from either sulfide or silicate-oxide ores, which generally contain no more than 3% nickel. Magmatic sulfide ores are mined underground or by open-pit methods. Pentlandite ($[NiFe]_9S_8$) is the principal sulfide ore; the largest known deposit is in Ontario, Canada, and substantial deposits are found in Minnesota, South Africa, Russia, Finland, and western Australia. Silicate-oxide ores, or garnierites, originate in (current or former) humid tropical regions and are surface mined by open-pit methods (IARC 1990, ATSDR 1997). Primary nickel production from mines in the United States was steady from the late 1950s to 1980, ranging from 22 million to 31 million pounds per year (USGS 2010). After 1980, primary production of nickel in the United States started declining, and no primary production has occurred since 1998, when 9.5 million pounds was produced.

Recycled scrap metal accounts for a large part of the nickel supply; in addition, relatively small quantities of nickel are recovered as a by-product at copper and precious-metal refineries or from reclamation of spent catalysts (Kuck 2009). Production from these secondary sources increased steadily from 46 million pounds in 1970 to a high of 234 million pounds in 2006, then declined to 140 million pounds in 2009.

From 1980 to 2009, U.S. consumption of nickel ranged from 335 million to 551 million pounds; consumption was highest in 2006 (Kuck 2010, USGS 2010). The demand for nickel is due in part to increasing use of nickel-based batteries and nickel-bearing superalloys used in aircraft engines (Kuck 2009), with the United States being dependent on imports of most nickel supplies.

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Category	Year	Quantity (million lb)
Production + imports[a]	2015	500 to 750
U.S. imports[b]	2017	420.7
U.S. exports[b]	2017	183.4

Sources: [a]EPA 2016. [b]USITC 2018 (reported as "nickel and articles thereof").

Exposure

Environmental exposure to nickel occurs through inhalation, ingestion, and dermal contact. The general population is exposed to low levels of nickel because it is widely present in air, water, food, and consumer products. The general population takes in most nickel through food; the average daily intake from food in the United States is estimated at 150 to 168 µg. Typical daily intake from drinking water is 2 µg and from air is 0.1 to 1 µg. The general population is also exposed to nickel in nickel alloys and nickel-plated materials, such as coins, steel, and jewelry, and residual nickel may be found in soaps, fats, and oils (ATSDR 1997).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, releases of nickel to the environment trended downwards from 1988 to 2003 and then increased, while releases of nickel compounds increased until 1998 but have since decreased by half. In 2007, 1,552 facilities released 8.3 million pounds of nickel, and 1,027 facilities released 30.5 million pounds of nickel compounds (TRI 2009).

Occupational exposure to nickel occurs mainly through inhalation of dust particles and fumes or through dermal contact. Nickel workers can also ingest nickel-containing dusts. Occupational exposure is common for workers involved in mining, smelting, welding, casting, spray-painting and grinding, electroplating, production and use of nickel catalysts, polishing of nickel-containing alloys, and other jobs where nickel and nickel compounds are produced or used (HSDB 2009). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 23,272 workers potentially were exposed to nickel and nickel compounds (NIOSH 1976), and the National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 507,681 workers, including 19,673 women, potentially were exposed to nickel (molecular formula unknown) (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Nickel carbonyl, nickel cyanide, nickel nitrate, and nickel nitrite are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials; nickel picrate is forbidden from transport.

Nickel carbonyl, nickel cyanide, and nickel tetracarbonyl are considered marine pollutants and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Nickel compounds are listed as mobile-source air toxics for which regulations are to be developed.

National Emission Standards for Hazardous Air Pollutants: Nickel and its compounds are listed as hazardous air pollutants.

Prevention of Accidental Release: Threshold quantity (TQ) = 1,000 lb for nickel carbonyl.

Urban Air Toxics Strategy: Nickel compounds are identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Biosolids Rule: Limits have been established for nickel in biosolids (sewage sludge) when used or disposed of via land application, surface disposal, or incineration.

Effluent Guidelines: Nickel and nickel compounds are listed as toxic pollutants.

Water Quality Criteria: Based on fish or shellfish and water consumption = 610 µg/L for metallic nickel; based on fish or shellfish consumption only = 4,600 µg/L for metallic nickel.

Numerous nickel compounds are designated as hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb for nickel, nickel ammonium sulfate, nickel chloride, nickel nitrate, and nickel sulfate; 10 lb for nickel carbonyl, nickel cyanide, and nickel hydroxide.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Nickel and nickel compounds are listed substances subject to reporting requirements.

Threshold planning quantity (TPQ) = 1 lb for nickel carbonyl.

Reportable quantity (RQ) = 10 lb for nickel carbonyl.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of nickel or nickel compounds = P073, P074, F006.

Nickel and nickel compounds are listed as hazardous constituents of waste.

Food and Drug Administration (FDA, an HHS agency)

Maximum permissible level of nickel in bottled water = 0.1 mg/L.

The color additives ferric ammonium ferrocyanide and ferric ferrocyanide, when used in drugs, may contain nickel at levels no greater than 200 ppm.

Menhaden oil may contain nickel at concentrations not to exceed 0.5 ppm.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2018, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 1 mg/m^3 for elemental nickel and compounds other than nickel carbonyl; = 0.001 ppm (0.007 mg/m^3) for nickel carbonyl.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value - time-weighted average (TLV-TWA) = 1.5 mg/m^3 for elemental nickel; = 0.1 mg/m^3 for soluble inorganic nickel compounds and nickel subsulfide; = 0.2 mg/m^3 for insoluble inorganic nickel compounds).

Threshold limit value – ceiling (TLV-C) = 0.05 ppm for nickel carbonyl.

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Recommended exposure limit (REL) = 0.015 mg/m^3 for elemental nickel and nickel compounds other than nickel carbonyl; = 0.001 ppm (0.007 mg/m^3) for nickel carbonyl.

Immediately dangerous to life and health (IDLH) limit = 10 mg/m^3 for elemental nickel and nickel compounds other than nickel carbonyl; = 2 ppm (14 mg/m^3) for nickel carbonyl.

Metallic nickel and nickel compounds are listed as potential occupational carcinogens.

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Cobalt-Related Exposures

The Report on Carcinogens includes two separate listings (i.e., profiles) for cobalt-related exposures: Cobalt and Cobalt Compounds That Release Cobalt Ions *In Vivo* and Cobalt-Tungsten Carbide: Powders and Hard Metals. Cobalt and cobalt compounds as a class are listed for the first time in the *Fourteenth Report on Carcinogens,* and this listing includes and supersedes the listing for cobalt sulfate, which first appeared in the *Eleventh Report on Carcinogens*. Cobalt–tungsten carbide was first listed in the *Twelfth Report on Carcinogens*. The profiles for these listings follow this introduction.

Cobalt and Cobalt Compounds That Release Cobalt Ions *In Vivo*

CAS No. 7440-48-4 (Cobalt metal)

No separate CAS No. assigned for cobalt compounds as a class

Reasonably anticipated to be human carcinogens

First listed in the *Fourteenth Report on Carcinogens* (2016)

Introduction

This listing of the class of cobalt and cobalt compounds that release cobalt ions *in vivo* (as defined below) supersedes the previous listing of cobalt sulfate in the Report on Carcinogens. The compound cobalt sulfate was first listed in the *Eleventh Report on Carcinogens* in 2004 as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals.

Carcinogenicity

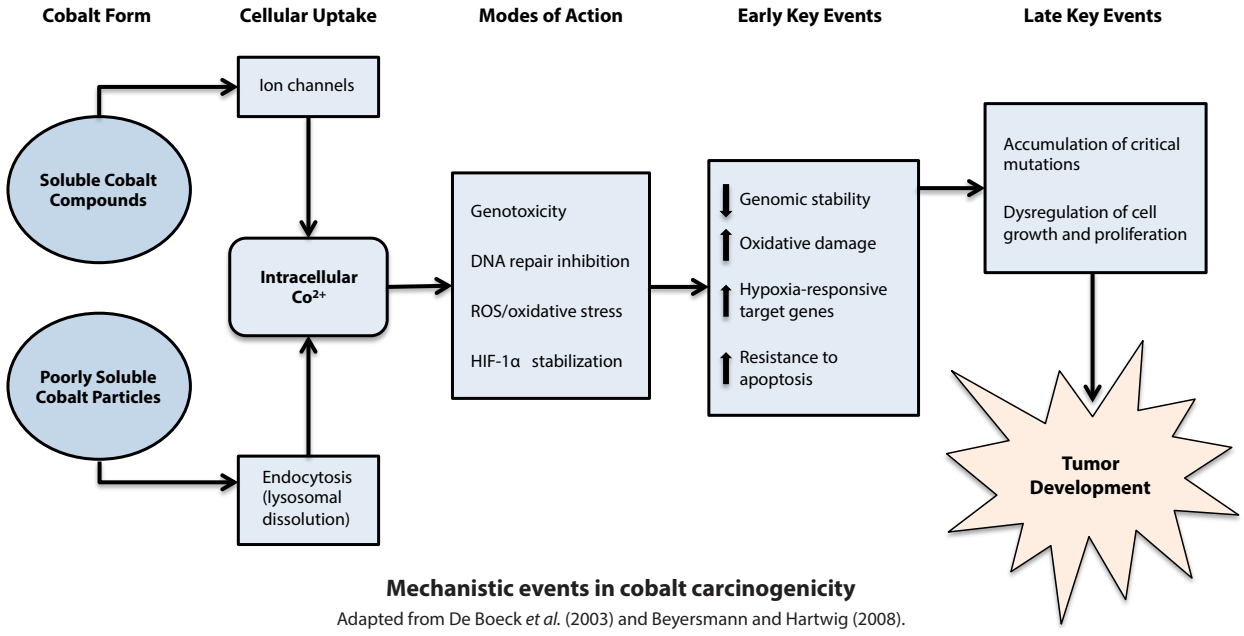
Cobalt and cobalt compounds that release cobalt ions *in vivo* are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting data from studies on mechanisms of carcinogenesis. Mechanistic data indicate that the release of cobalt ions *in vivo* is a key event for cobalt-induced carcinogenicity. The available data show that cobalt metal and cobalt compounds that release cobalt ions *in vivo* (regardless of their solubility in water) act via similar modes of action to cause similar types of effects, including cell death, DNA damage, and cancer, and that the cobalt ion is largely responsible for the toxicity and carcinogenicity (NTP 1998, 2014, IARC 2006).

Both water-soluble cobalt compounds and poorly water-soluble cobalt particles are included in this class, as both types of cobalt species can release cobalt ions in vivo, although they differ in the mechanisms by which the cobalt ions enter cells. Vitamin B_{12}, which is an essential cobalt-containing nutrient, does not meet the criteria for this listing, because the vitamin does not release cobalt ions, but passes through the body intact while bound to specific carrier proteins (Neale 1990). It is not possible to determine the quantitative carcinogenic risk from cobalt ions released from surgical implants because of limitations in the available cancer studies of cobalt alloy implants in experimental animals and of patients with cobalt-containing surgical implants.

Mechanisms of Carcinogenesis and Other Relevant Data

The key events related to toxicity and carcinogenicity are thought to include cellular uptake of cobalt, intracellular release of cobalt ions from particles, and immediate and downstream biological responses related to the proposed modes of action. The first step in the carcinogenicity or toxicity process is the release of cobalt ions *in vivo*. Water-soluble cobalt compounds release cobalt ions into fluids outside the cell, and the ions enter the cell through ion channels within the cell membrane. In contrast, poorly soluble particulate cobalt compounds are taken up by specific organelles (lysosomes) in the cell via a process called endocytosis; cobalt is then solubilized in the acidic environment in the lysosomes, and the ions are released inside the cell. Evidence for cellular uptake of the different forms of cobalt is provided by studies evaluating their solubility in biological fluids *in vitro* (e.g., in gastric and lysosomal fluids) (see Properties) and *in vitro* studies measuring levels of cobalt ions within cells (Peters *et al.* 2007, Ortega *et al.* 2014, Sabbioni *et al.* 1994, Smith *et al.* 2014).

Although the mechanism(s) of action for cobalt-induced carcinogenic effects are not completely understood, several key events have been identified that are related to biologically plausible modes of action and are applicable to all cobalt forms that release cobalt ions *in vivo.* These events include inhibition of DNA repair, genotoxicity, generation of reactive oxygen species (ROS) resulting in oxidative damage, and stabilization of hypoxia-inducible factor 1α (HIF-1α), a protein that increases the expression of genes that promote sur-



Mechanistic events in cobalt carcinogenicity

Adapted from De Boeck *et al.* (2003) and Beyersmann and Hartwig (2008).

vival of cells when they receive less oxygen. The proposed modes of action are summarized in the diagram below.

Cobalt is considered to be a clastogen, because in *in vitro* assays in mammalian cells, it primarily causes chromosome damage and DNA strand breaks. Only a few genotoxicity studies in experimental animals were available, but the results were generally consistent with those of *in vitro* studies. Two potential mechanisms for genotoxicity include (1) direct induction of oxidative damage to DNA by cobalt(II) ions and (2) an indirect effect through inhibition of DNA repair (Smith *et al.* 2014, Lison 2015).

Cobalt is one of a group of metals (transition metals, like iron and nickel) that promote oxidation and reduction (redox) reactions through transfer of electrons. *In vitro* studies have shown that cobalt particles and ions can induce ROS in mammalian cells, with cobalt metal and cobalt oxide particles having a greater effect than ions. It has been proposed that ROS can play a role in the tumor development process at several stages, including initiating the process by inducing mutations and promoting proliferation of these mutated cells by deregulating controls on cell growth, leading to tumors. Studies in rats have shown that cobalt causes oxidative stress and oxidative DNA damage in several tissues, including kidney, liver, and lung (Kasprzak *et al.* 1994), which supports this proposed pathway for cobalt-induced carcinogenicity. Also, a higher frequency of a specific mutation in the K-*ras* oncogene, a gene with the potential to cause cancer, was found in cobalt-induced lung tumors in mice and rats than in spontaneous lung tumors (NTP 1998, 2014, IARC 2006). This mutation involves substitution of one nucleotide for another in a G to T transversion, which is a mutation commonly associated with oxidative DNA damage. In addtion, cobalt-induced oxidative stress (via the production of ROS) can activate genes and proteins (specifically, the transcription factors NF-κB, AP1, p53, and Nrf2) that in turn regulate the expression of many genes that play a role in carcinogenicity, such as those involved in inflammation and control of the cell cycle (Valko *et al.* 2005, 2006, Beyersmann and Hartwig 2008, Shukla *et al.* 2012, Davidson *et al.* 2015, PubChem 2015).

Finally, a well-established biological effect of cobalt is to mimic oxygen deficiency in cells by stabilizing HIF-1α (Maxwell and Salnikow 2004, Greim *et al.* 2009, Saini *et al.* 2010a,b, Galán-Cobo *et al.* 2013, Gao *et al.* 2013, Nyga *et al.* 2015). HIF-1α plays a central role in regulating more than 100 hypoxia-responsive genes and is a major regulator of the adaptation of cancer cells to oxygen deficiency. HIF-1α overexpression has been linked to cancer initiation and progression and is a common characteristic of many human cancers (Paul *et al.* 2004, Galanis *et al.* 2008, 2009, Cheng *et al.* 2013).

Although most of the toxicological effects of cobalt are attributed to the cobalt ion, direct toxic effects of cobalt particles also contribute, as evidenced by the greater toxicity of cobalt metal than of cobalt sulfate in National Toxicology Program (NTP) rodent bioassays (NTP 1998, 2014, Behl *et al.* 2015). Differences in the relative toxicity reported for cobalt particles and ions may be partially explained by differences in the mechanisms by which cobalt enters the cell and in the subsequent accumulation and distribution of cobalt within the cell, as well as a synergistic effect between the particles and metal on ROS production (Peters *et al.* 2007, Sabbioni *et al.* 2014, Smith *et al.* 2014).

Cancer Studies in Experimental Animals

Exposure of experimental animals to cobalt metal or cobalt compounds caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. This conclusion is based on studies in rats and mice exposed to cobalt metal (five studies), water-soluble cobalt compounds (two studies with cobalt sulfate and one study with cobalt chloride), and poorly water-soluble cobalt compounds (four studies with cobalt oxide). Studies of cobalt alloys and radioactive cobalt in experimental animals were not considered to be informative, because of potential confounding by other carcinogens.

Inhalation exposure of rats and mice to cobalt metal (NTP 2014) or cobalt sulfate (NTP 1998) or intratracheal instillation of cobalt oxide in rats (Steinhoff and Mohr 1991) caused lung tumors (alveolar/bronchiolar adenoma and carcinoma). In addition, inhalation exposure of rats to cobalt metal caused squamous-cell tumors of the lung (primarily cystic keratinizing epithelioma) in females and possibly in males.

In inhalation studies of cobalt metal in rats (NTP 2014), tumors were also induced at sites distant from the lung, including tumors of the pancreas (islet-cell adenoma or carcinoma combined) in males and of the hematopoietic system (mononuclear-cell leukemia) in females, indicating a systemic effect. Increased incidences of kidney tumors (adenoma or carcinoma combined) in male rats and pancreas (carcinoma) in female rats may have been related to cobalt metal inhalation; however, the findings were not conclusive. Inhalation exposure to cobalt metal (NTP 2014) or cobalt sulfate (NTP 1998) induced adrenal-gland tumors (benign and malignant pheochromocytoma), which could have been caused by direct or indirect mechanisms.

In rats, local injection of cobalt at various anatomic locations caused tumors at the injection sites. Although these studies were less robust than the inhalation studies, and sarcomas are common in rats following injection of a variety of compounds, the consistency of the tumor types and findings across different cobalt forms provides supporting evidence for the carcinogenicity of cobalt. Intraperitoneal or intramuscular injection of the poorly water-soluble compound cobalt oxide caused histiocytoma or sarcoma at the injection site (Gilman and Ruckerbauer 1962, Steinhoff and Mohr 1991), and subcutaneous injection of the water-soluble compound cobalt chloride caused fibrosarcoma (Shabaan *et al.* 1977). Intramuscular or intrathoracic injection of cobalt metal (Heath 1956, Heath and Daniel 1962) or nanoparticles (Hansen *et al.* 2006) caused various types of sarcoma (primarily rhabdomyofibrosarcoma, rhabdomyosarcoma, or fibrosarcoma). In the study of nanoparticles, no tumors were observed after implantation of substances (e.g., titanium dioxide and silicon dioxide) with the same physical characteristics (i.e., surface-to-volume ratio) as cobalt, suggesting that the tumors were due to carcinogenic properties of cobalt and not just to a reaction to any physical implant.

A few studies in rodents (Gilman and Ruckerbauer 1962, Jasmin and Riopelle 1976, Wehner *et al.* 1977) found no tumors at certain tissue sites following exposure to the same forms of cobalt that caused tumors in other studies; however, these studies generally lacked sensitivity to detect an effect, because of the use of a less sensitive animal model, shorter study duration, or lower exposure levels.

Cancer Studies in Humans

The data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure specifically to cobalt and cobalt compounds that release cobalt ions *in vivo*. The data relevant to the evaluation were from studies primarily evaluating lung cancer in five independent cohorts of workers in different types of industries and two population-based case-control studies of esophageal cancer and other cancers of the respiratory and upper digestive (aerodigestive) tract, one in Ireland (O'Rorke *et al.* 2012) and the other in the state of Washington (Rogers *et al.* 1993). Studies of cobalt alloys in humans (primarily joint implants) were not considered to be informative, because they were not specific to cobalt exposure, and the extent of any cobalt exposure was unknown.

Although increased risks of lung cancer were found in most of the cohort studies, it is unclear that the excess risks were due to exposure specifically to cobalt, because of potential confounding from exposures to known lung carcinogens or other study limitations. In the cohort studies, hard-metal (Moulin *et al.* 1998, Wild *et al.* 2000) and nickel-refinery workers (Grimsrud *et al.* 2005) were also exposed to known lung carcinogens. The findings of an increased risk of lung cancer among porcelain painters exposed to cobalt was complicated by a somewhat similar increase in risk among female pottery workers who were not thought to be exposed to cobalt (Tüchsen *et al.* 1996). In studies of a cohort of cobalt production workers, the excess risk found in the first report of this cohort (Mur *et al.* 1987) was no longer present in an update of the cohort (Moulin *et al.* 1993). No association between cobalt exposure and lung cancer was found in a study of stainless- and alloyed-steel workers in France (Moulin *et al.* 2000). Most of the studies had limited sensitivity to detect a true risk, because of small numbers of lung-cancer cases among exposed workers, crude methods of exposure assessment, or potential healthy-worker-related effects (due to the fact that workers are healthier on average than the general population).

Increased risks of esophageal cancer were suggested in two case-control studies; however, it is unclear whether cobalt exposure contributed to the cancer excess. In both studies, cobalt exposure was assessed from a single sample of toenail clippings taken at or several months after diagnosis of esophageal cancer. Measurements of cobalt in toenails reflect an integrated exposure that occurred 12 to 18 months before clipping, raising the question of whether levels found in toenails close to or, in many cases, after cancer diagnosis reflected the relevant period of exposure for long-latency cancer.

Properties

As a class, cobalt and cobalt compounds that release cobalt ions *in vivo* are related largely by their chemical properties, specifically bioavailability. (The different valence states of cobalt are described below, under Chemical Characteristics.)

Bioavailability

The carcinogenic and toxic effects of cobalt and cobalt compounds begin with the release of cobalt ions *in vivo*. The bioavailability of a metal species can be predicted by its solubility in biological fluids, such as synthetic equivalents of gastric and intestinal fluids (for ingestion exposure) or lung (alveolar, interstitial, and lysosomal) fluids (for inhalation exposure), and by studies in cultured cells. Results from studies testing solubility in synthetic biological fluids are shown in the table below, along with other chemical and physical properties of cobalt metal and these cobalt compounds. These studies demonstrated that cobalt metal and both water-soluble and poorly water-soluble cobalt compounds can dissolve and release cobalt ions in some biological fluids (Brock and Stopford 2003, Stopford *et al.* 2003, Cobalt Development Institute personal communication 21 Jul and 19 Oct 2015), suggesting that they will release ions *in vivo*.

Very low values (≤ 2%) for bioaccessibility have been reported for the sulfide and mixed (II,III) oxide (Co_3O_4), and intermediate values (14% to 55%) for stearate and oxalate under the same test conditions. However, other, more informative tests with more physiologically relevant test conditions (e.g., two-week studies with 0.3-µm particles in culture medium in the presence of alveolar macrophages) have reported 50% solubility for Co_3O_4. In addition, Ortega *et al.* (2014) found that intracellular concentrations of solubilized cobalt ions were

Physical and chemical properties of cobalt metal and some cobalt compounds

Form[a]	CAS No.	Formula	Molec. weight	Physical form	Density or specific gravity	Water solubility (g/100 cc)[b]	Bioaccessibility (% solubility in gastric/lysosomal fluids)
Cobalt metal	7440-48-4	Co[c]	58.9[c]	grey hexagonal or cubic metal[c]	8.92[c]	0.00029[d]	100/100[e]
Water-soluble compounds							
Acetate (org.)	71-48-7	$Co(C_2H_2O_2)2$[f]	249.1[f]	red-violet, monoclinic[f]	1.70[f]	34.8[d]	98/80[d]
Chloride	7646-79-9	$CoCl_2$[g]	129.8[g]	blue hexagonal leaflets[g]	3.36[g]	45[g]	100/100[e]
Nitrate	10141-05-6	CoN_2O_6[c]	182.9[c]	red powder or crystals[c]	2.49[c]	67.0[d]	96/100[d]
Sulfate heptahydrate	10026-24-1	$CoSO_4•7H_2O$[f]	281.1[f]	red pink, monoclinic[f]	1.95[f]	60.4[f]	100/100[e]
Poorly water-soluble compounds							
Carbonate (org.)	513-79-1	$CoCO_3$[f]	118.9[f]	red, trigonal[f]	4.13[f]	0.00114[d]	100/100[e]
2-Ethylhexanoate (org.)	136-52-7	$Co(C_8H_{15}O_2)_2$[f]	173.7[h]	blue liquid (12% Co)[f]	1.01[f]	0.630[d]	100/100[e]
Hydroxide	21041-93-0	$Co(OH)_2$[f]	93.0[f]	rose-red, rhombic[f]	3.60[f]	0.00032[f]	95/98[d]
Naphthenate (org.)	61789-51-3	$Co(C_{11}H_7O_2)_2$[c]	401.3[c]	purple liquid (6% Co)[f]	0.97[f]	0.0293[d]	100/100[e]
Oxalate (org.)	814-89-1	CoC_2O_4[f]	147.0[f]	white or reddish[f]	3.02[f]	0.00322[d]	37/55[d]
Oxide	1307-96-6	CoO[f]	74.9[f]	green-brown cubic[f]	6.45[f]	0.00049[d]	100/92.4[e]
(II,III) Oxide	1308-06-1	Co_3O_4[f]	240.8[f]	black, cubic[f]	6.07[f]	0.00016[d]	2/2[d] (50%)[i]
Propionate (org.)	1560-69-6	$Co(C_3H_5O_2)_2$[c]	205.1[c]	reddish solid[d]	–	7.49[d]	91/94[d]
Stearate (org.)	1002-88-6	$Co(C_{18}H_{35}O_2)_2$[c]	625.9[c]	grey solid[d]	–	0.00705[d]	14/16[d]
Sulfide	1317-42-6	CoS[f]	91.0[f]	reddish octahedral[f]	5.45[f]	0.00038[f]	1/1[d]

[a]Cobalt compounds selected for inclusion in the table are those with toxicological data or of commercial importance. All compounds contain Co(II) except where noted. Forms in italics have been tested for carcinogenicity or genetic toxicity or have mechanistic data; org. = organic compound; all others are inorganic.
[b]Solubility data were converted to grams per 100 cubic centimeters as necessary.
[c]PubChem 2015, [d]Cobalt Development Institute personal communication 21 Jul and 19 Oct 2015, [e]Stopford *et al.* 2003, [f]CDI 2006, [g]HSDB 2012, [h]HSDB 2004.
[i]Kreyling *et al.* 1990. Bioaccessibility was assessed by release of cobalt ions into culture medium in the presence of canine alveolar macrophages after two weeks of culture.

similar for Co_3O_4 and cobalt chloride in human lung cells *in vitro*, suggesting that Co_3O_4 would release cobalt ions *in vivo.* Results with other biological fluids, such as serum and intestinal, alveolar, and interstitial fluids, indicate that the species of cobalt compound, particle size and surface area, and pH of the surrogate fluid all can affect the solubility of cobalt in biological fluids.

The solubility of cobalt compounds in water depends largely on pH, and cobalt is generally more mobile in acidic solutions than in alkaline solutions (IARC 1991, Paustenbach *et al.* 2013). Sulfates, nitrates, and chlorides of cobalt tend to be soluble in water, whereas oxides (including the mixed oxide, Co_3O_4), hydroxides, and sulfides tend to be poorly soluble or insoluble in water (Lison 2015). Organic cobalt compounds can be either soluble, as is cobalt(II) acetate, or insoluble, as are cobalt(II) carbonate and cobalt(II) oxalate (CDI 2006). In addition to low pH, solubilization of some poorly water-soluble compounds in biological fluids may be enhanced in the presence of binding proteins (IARC 2006).

Chemical Characteristics

Cobalt (Co) is a naturally occurring transition element with magnetic properties. It is the 33rd most abundant element, making up approximately 0.0025% of the weight of Earth's crust. Cobalt is a component of more than 70 naturally occurring minerals, including arsenides, sulfides, and oxides. The only stable and naturally occurring cobalt isotope is ^{59}Co (ATSDR 2004, WHO 2006). Metallic cobalt, Co(0), exists in two crystalline forms, hexagonal and cubic, which are stable at room temperature (IARC 1991, ATSDR 2004, WHO 2006). Cobalt predominantly occurs in two oxidation states, Co(II) and Co(III). Co(II) is much more stable than Co(III) in aqueous solution (Nilsson *et al.* 1985, Paustenbach *et al.* 2013) and is present in the environment and in most commercially available cobalt compounds (e.g., cobalt chloride, sulfide, and sulfate). Co(III) also is present in some commercially available cobalt compounds, including the mixed oxide (Co_3O_4) (IARC 1991, Paustenbach *et al.* 2013, Lison 2015) and some simple salts of Co(III) (e.g., Co_2O_3). Important salts of carboxylic acids include formate, acetate, citrate, naphthenate, linoleate, oleate, oxalate, resinate, stearate, succinate, sulfamate, and 2-ethylhexanoate.

Use

Cobalt and cobalt compounds are used in numerous commercial, industrial, and military applications. On a global basis, the largest use of cobalt is in rechargeable battery electrodes (Shedd 2014b); however, U.S. production of rechargeable batteries has been very limited (Brodd 2005). In 2012, the reported U.S. consumption of cobalt and cobalt compounds was approximately 8,420 metric tons, the majority used for superalloys (Shedd 2014b). Major uses for metallic cobalt include production of superalloys, cemented carbides, and bonded diamonds. Cobalt nanoparticles are used in medical applications (e.g., sensors, magnetic resonance imaging contrast enhancement, and drug delivery), and cobalt nanofibers and nanowires are used in industrial applications. Cobalt compounds are used as pigments for glass, ceramics, and enamels (oxides, sulfate, and nitrate), as driers for paints, varnishes, or lacquers (hydroxide, oxides, propionate, acetate, tallate, naphthenate, and 2-ethylhexanoate), as catalysts (hydroxide, oxides, carbonate, nitrate, acetate, oxalate, and sulfide), as adhesives and enamel frits (naphthenate, stearate, and oxides), and as trace mineral additives in animal diets (carbonate, sulfate, nitrate, oxides, and acetate). U.S. consumption of cobalt and cobalt compounds in 2012 is summarized in the following table.

The fastest-growing use for cobalt in recent years has been in high-capacity, rechargeable batteries, including nickel-cadmium, nickel-metal hydride, and lithium-ion batteries for electric vehicles and portable electronic devices such as smartphones and laptops (Maverick 2015). Many other uses for cobalt exist, including in integrated circuit contacts and semiconductor production. An emerging use is as a key element in several forms of "green" energy technology applications, including gas-to-liquids and coal-to-liquids processes, oil desulfurization, clean coal, solar panels, wind and gas turbines, and fuel cells, and in cobalt-based catalysts for sunlight-driven water-splitting to convert solar energy into electrical and chemical energy.

End use	Metric tons of cobalt content	Percent of total consumption
Superalloys	4,040	48.0
Chemicals and ceramics	2,300	27.3
Cemented carbides	774	9.2
Other alloys[a]	699	8.3
Steels	548	6.5
Miscellaneous and unspecified	63	0.7

Source: Shedd 2014b.
[a]Includes magnetic, nonferrous, and wear-resistant alloys and welding materials.

Production

Cobalt metal is produced as a by-product from ores associated with copper, nickel, zinc, lead, and platinum-group metals and is most often chemically combined in its ores with sulfur and arsenic (Davis 2000, CDI 2006). The largest cobalt reserves are in the Congo (Kinshasa), Australia, Cuba, Zambia, Canada, Russia, and New Caledonia, with very limited production in the United States in recent years (Shedd 2014a). Except for a negligible amount of by-product cobalt produced from mining and refining of platinum-group metal ores, the United States did not refine cobalt in 2012 (Shedd 2014b). Cobalt has not been mined in the United States in over 30 years (ATSDR 2004); however, a primary cobalt mine, mill, and refinery were being established in Idaho in 2015 (Farquharson 2015). In 2012, 2,160 metric tons of cobalt was recycled from scrap. No cobalt has been sold from the National Defense Stockpile since 2009.

Metallic cobalt and several cobalt compounds are high-production-volume chemicals, based on their annual production or importation into the United States in quantities of at least 1 million pounds. Volumes of U.S. production, imports, and exports of cobalt metal and high-production-volume cobalt compounds are listed in the following table.

	Quantity (lb)		
Cobalt category	Production (2015)	Imports (2017)	Exports (2017)
Metal (excluding alloys)	10 million to 50 million	–	–
Compounds			
Acetates	1 million to 10 million	434,399	438,720
Carbonates	1 million to 10 million	–	–
Chlorides	1 million to 10 million	79,657	12,890
2-Ethylhexanoate	1 million to 10 million	–	–
Hydroxide	1 million to 10 million	–	–
Oxides	1 million to 10 million[a]	4,663,291[b]	441,396[b]
Propionate	1 million to 10 million	–	–

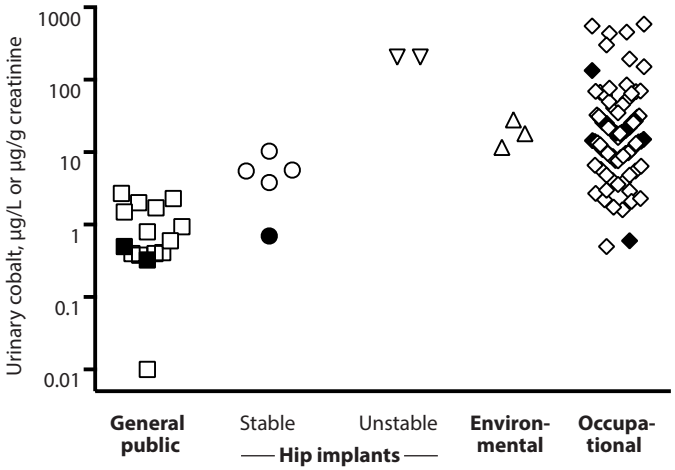
Sources: EPA 2016 (production volume = production + imports), USITC 2018 (imports and exports).
– = no data found.
[a]The reported value is for cobalt oxide (CoO).
[b]The reported value is for cobalt hydroxide and oxides combined.

Exposure

A significant number of people living in the United States are exposed to cobalt, based on several lines of evidence, including biological monitoring data demonstrating exposure in occupationally and non-occupationally exposed populations. Data from the U.S. Envi-

ronmental Protection Agency's Toxics Release Inventory (TRI) indicate that production- and use-related releases of cobalt compounds have occurred at numerous industrial facilities in the United States.

In biomonitoring studies that measured cobalt in the urine of people exposed to cobalt from various sources, the highest levels generally were due to occupational exposures and failed hip implants; lower levels were due to exposure from normal implants or the environment. The lowest levels were observed in the general population (with unknown sources of exposure). The graph below shows the mean or median levels of urinary cobalt for the general population and for groups with known exposures. Data are reported for both U.S. and non-U.S. exposures; occupational and medical implant exposures outside the United States can be informative because of the similarity of production methods and implant compositions worldwide.



Urine levels of cobalt for various exposed groups

Source: NTP 2015.
Filled symbols = U.S. data; open symbols = non-U.S. data.
Each data point represents a different study.

Urinary cobalt measurements in the U.S. general population were similar in 1999 and 2014, with geometric mean values between 0.316 and 0.391 µg/L, according to the National Health and Nutrition Examination Survey (CDC 2018). Urinary cobalt is considered a good indicator of absorbed cobalt (IARC 2006, WHO 2006), especially from recent exposures (ATSDR 2004). Levels of cobalt in blood (including whole blood, plasma, and serum) show a pattern similar to that for urinary cobalt levels (CDC 2018).

Occupational Exposure

The primary route of occupational exposure to cobalt is via inhalation of dust, fumes, mists, or gaseous cobalt carbonyl. Dermal contact with cemented carbide (i.e., hard-metal) powders and cobalt salts can result in systemic uptake. Occupational exposure to cobalt occurs in the following industries: (1) production of cobalt metal or salts, (2) metallurgical-related industries, (3) cemented carbides and bonded diamonds, (4) chemicals and pigments, and (5) electronics, "green" energy, and recycling. Occupational exposure has been documented by measurements of cobalt in ambient workplace air (as shown in the following table) and in blood, urine (as shown in the figure above), nails, and hair, and lung tissue from workers or deceased workers (IARC 1991, ATSDR 2004, IARC 2006, CDC 2013). The highest levels of cobalt in workplace air were generally for hard-metal manufacture involving cobalt metal powders (> 1,000 µg/m^3 in some instances) (NTP 2009), production of cobalt salts, and metallurgical-related industries (> 10,000 µg/m^3 in some instances) (IARC 2006). The highest cobalt levels in urine, blood, hair, and nails also were associated with exposure to cobalt powders.

Industry	Cobalt in workplace air (range, µg/m^3)
Production of cobalt metal or salts	2–50,000
Metallurgical-related industries[a]	ND–21,000[b]
Cemented carbides and bonded diamonds[a]	ND–1,622
Chemicals and pigments[a]	ND–80
Electronics, "green" energy, and recycling[a]	ND–10

Sources: IARC 2006, NIOSH 2015. ND = not detected.
[a]The range for cobalt in workplace air includes U.S. data from NIOSH Hazard Evaluation and Technical Assistance surveys.
[b]One higher value was reported; however, the Occupational Safety and Health Administration noted that the sample appeared to have been tampered with.

Surgical Implants

Total hip implants consist of (1) a femoral head attached to a stem that is inserted in the thigh bone (usually made of ceramic or metal) and (2) a socket or cup that is anchored in the pelvis (made of metal, ceramic, or polyethylene). Cobalt-chromium-molybdenum (CoCrMo) alloy is the predominant alloy used in metal-containing implants, such as metal-on-metal implants (in which both articulating surfaces are metal), polyethylene-on-metal implants, and metal-on-ceramic implants. Other metals, such as nickel, tungsten, iron, aluminum, and titanium, may also be used in implants. Knee implants may also contain cobalt metal; however, unlike some hip implants with metal-to-metal contact, knee implants are designed so that metal surfaces do not contact each other. Cobalt ions may be released into the body throughout the lifetime of a cobalt-containing device (Sampson and Hart 2012, Devlin *et al.* 2013). Urinary levels of cobalt identified from studies of hip implants reported as stable or that did not specifically address stability ranged from approximately 0.7 to 12 µg/L, compared with a range of 0.01 to 4.2 µg/L for the general population (as shown in the previous graph). Implants may fail because of excessive wear or corrosion by body fluids, increasing the levels of cobalt released from the implants (Sampson and Hart 2012). Dunstan *et al.* (2005) reported blood cobalt levels of 19 and 52 µg/L in two individuals with unstable (radiologically loose) metal-on-metal implants. In rare cases, high levels of cobalt from failed implants may be associated with toxicity. Recommended levels of blood cobalt for further clinical investigation and action were set at 7 µg/L in the United Kingdom (MHRA 2012) and 10 µg/L in the United States by the Mayo Clinic (2015).

Environmental Exposure

The TRI reported that in 2013, on- and off-site industrial releases of cobalt and cobalt compounds totaled approximately 5.5 million pounds from 723 facilities in the United States (TRI 2014a). Calculations based on media-specific release data from the TRI indicate that releases to land accounted for 82% of total releases in 2013 (TRI 2014b,c). Worldwide, approximately 75,000 metric tons of cobalt enters the environment annually, with similar amounts coming from natural sources (40,000 metric tons) and sources related to human activities (35,000 metric tons) (Shedd 1993, CDI 2006). Recycling of electronic and electrical waste can result in release of cobalt to the environment; however, releases from this source are less of a concern in the United States than in other global regions where recycling is more common and less controlled (Julander *et al.* 2014).

The average concentration of cobalt in ambient air in the United States has been reported to be approximately 0.4 ng/m^3 (ATSDR 2004). Levels can be orders of magnitude higher near source areas (e.g., near facilities processing cobalt-containing alloys and compounds) reported from outside the United States. The median co-

balt concentration in U.S. drinking water has been reported to be less than 2.0 µg/L; however, levels as high as 107 µg/L have been reported (ATSDR 2004). Cobalt concentrations have been reported to range from 0.01 to 4 µg/L in seawater and from 0.1 to 10 µg/L in fresh water and groundwater (IARC 2006). Studies have reported cobalt soil concentrations ranging from 0.1 to 50 ppm. However, soils near ore deposits, phosphate rock, or ore-smelting facilities or soils contaminated by airport or highway traffic or near other source areas may contain higher concentrations (IARC 2006).

Data for individuals exposed to cobalt from the environment are limited, but a study of metal exposure from mining and processing of nonferrous metals in Katanga, Democratic Republic of Congo, found that geometric mean urinary cobalt concentrations were 4.5-fold higher for adults and 6.6-fold higher for children in urban and rural communities near mines and metal smelters than in rural communities without mining or industrial activities (Cheyns *et al.* 2014).

Other Sources of Exposure of the General Population

The general population can be exposed to low levels of cobalt primarily through consumption of food and to a lesser degree through inhalation of ambient air and ingestion of drinking water (ATSDR 2004). The daily cobalt intake from food in the United States was estimated to range from 3.4 to 11.6 µg based on analyses of 234 foods in the 1984 U.S. Food and Drug Administration Total Diet Study (Pennington and Jones 1987). Although this amount includes cobalt as part of both vitamin B_{12} and other cobalt compounds (ATSDR 2004), green, leafy vegetables and fresh cereals generally contain the most cobalt (IARC 1991), and these plant sources of cobalt do not contain vitamin B_{12}. In the 1960s, some breweries added cobalt salts to beer to stabilize the foam (resulting in cobalt exposures of 0.04 to 0.14 mg/kg of body weight), but cobalt is no longer added to beer (ATSDR 2004). Higher cobalt intake may result from consumption of over-the-counter or prescription mineral preparations containing cobalt compounds.

Other potential sources of exposure include consumer products and tobacco smoking. Cobalt is present in only a few consumer products, including cleaners, detergents, soaps, car waxes, and a nickel metal hydride battery (5% to 10% cobalt) (ATSDR 2004, HPD 2014). Various brands of tobacco have been reported to contain cobalt at concentrations ranging from less than 0.3 to 2.3 µg/g of dry weight, and 0.5% of the cobalt content is transferred to mainstream smoke (WHO 2006). However, urinary cobalt levels (unadjusted for creatinine) for cigarette-smoke-exposed and unexposed NHANES participants for survey years 1999 to 2004 did not differ significantly (Richter *et al.* 2009).

Regulations

Coast Guard (Dept. of Homeland Security)

Minimum requirements have been established for safe transport of cobalt naphthenate in solvent naphtha on ships and barges.

Department of Transportation (DOT)

Numerous cobalt compounds are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emission Standards for Hazardous Air Pollutants: Cobalt compounds are listed as hazardous air pollutants.

Clean Water Act

Cobalt discharge limits are imposed for numerous processes during the production of cobalt at secondary cobalt facilities processing tungsten carbide scrap raw materials.

Discharge limits for cobalt are imposed for numerous processes during the production of cobalt at primary cobalt facilities; for numerous processes during the production of batteries; and for numerous processes during the production of cobalt salts.

Discharge limits for cobalt are imposed for wastewater discharges from centralized waste treatment facilities except discharges and activities exempted in 40 CFR 437.1(b), (c), and 40 CFR 421, Subpart AC.

Cobaltous bromide, formate, and sulfamate are designated as hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1,000 lb for cobaltous bromide, formate, and sulfamate.

Emergency Planning and Community Right-To-Know Act

EPCRA Section 302: Threshold planning quantity (TPQ) = 100 lb for cobalt, ((2,2′-(1,2-ethanediylbis (nitrilomethylidyne))bis(6-fluorophenolato))(2-)-*N*,*N*′,*O*,*O*′)- (also called fluomine) (solids in powder form with particle size < 100 µm or solution or molten form); = 10,000 lb for all other forms of fluomine; = 10 lb for cobalt carbonyl (solids in powder form with particle size < 100 µm or solution or molten form); = 10,000 lb for all other forms of cobalt carbonyl.

EPCRA Section 304: Reportable quantity (RQ) = 100 lb for fluomine); = 10 lb for cobalt carbonyl.

Toxics Release Inventory: Cobalt and cobalt compounds are listed substances subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

Boiled linseed oil (containing no more than 0.33% manganese naphthenate and no more than 0.33% cobalt naphthenate) is exempt from the requirement of a tolerance when used as a coating agent for *S*-ethyl hexahydro-1*H*-azepine-1-carbothioate. No more than 15% of the pesticide formulation may consist of boiled linseed oil, and this exemption is limited to use on rice before edible parts form.

Food and Drug Administration (FDA, an HHS agency)

Cobaltous salts are prohibited from use in human food.

All drugs containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives) have been withdrawn from the market because they were found to be unsafe or not effective, and they may not be compounded.

Chromium–cobalt–aluminum oxide used as a color additive for linear polyethylene surgical sutures used in general surgery must comprise no more than 2% by weight of the suture material, not migrate to surrounding tissue, and conform to labeling requirements in 21 CFR 70.25.

Chromium cobalt-aluminum oxide may be used as a color additive in contact lenses in amounts not to exceed the minimum reasonably required to accomplish the intended coloring effect.

Ferric ammonium ferrocyanide and ferric ferrocyanide used to color externally applied drugs (including those for use in the area of the eye) must not contain more than 200 ppm cobalt (as Co) and conform to labeling requirements in 21 CFR 70.25.

21 CFR 369 contains recommended drug labeling statements for over-the-counter cobalt preparations containing ≥ 0.5 mg cobalt as a cobalt salt per dosage unit and which recommend administration rates of ≥ 0.5 mg per dose and ≥ 2 mg per 24-hour period.

An approved new drug application is required for marketing cobalt preparations intended for use by man.

21 CFR 872, 874, and 888 identify class designations (Class I, II, or III) of various cobalt-containing dental prosthetic device alloys, cobalt-chromium-alloy-based facial prosthetics, and cobalt-chromium-molybdenum orthopedic devices that determine the type of premarketing submission or application required for FDA clearance to market.

Cobalt naphthenate may be used in quantities that do not exceed those reasonably required as an accelerator in the production of cross-linked polyester resins used as articles or components of articles intended for repeated use in contact with food.

Cobalt aluminate may be safely used as a colorant in the manufacture of articles or components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding of food at levels not to exceed 5% by weight of all polymers except in resinous and polymeric coatings complying with 21 CFR 175.300, melamine-formaldehyde resins in molded articles complying with 21 CFR 177.1460, xylene-formaldehyde resins complying with 21 CFR 175.380, ethylene-vinyl acetate copolymers complying with 21 CFR 177.1350, and urea-formaldehyde resins in molded articles complying with 21 CFR 177.1900.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

This legally enforceable PEL was adopted from the 1968 ACGIH TLV-TWA shortly after OSHA was established; it may not reflect the most recent scientific evidence and may not adequately protect worker health.

Permissible exposure limit (PEL) (8-h TWA) = 0.1 mg/m^3 for cobalt metal, dust, and fume (as Co).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.02 mg/m^3 for cobalt and inorganic compounds; = 0.1 mg/m^3 for cobalt carbonyl and cobalt hydrocarbonyl.

Biological exposure index (BEI) = 15 µg/L for cobalt in urine for cobalt and inorganic compounds, including cobalt oxides but not combined with tungsten carbide, for end of shift at end of workweek.

Consumer Product Safety Commission (CPSC)

The CPSC has issued guidance regarding the potential hazards of specific cobalt- or cobalt-compound-containing art and craft materials (e.g., glazes, glass colorants, paints, toners, pigments, and dyes) and specific precautions to take when using them.

Environmental Protection Agency (EPA)

Regional Screening Levels (formerly Preliminary Remediation Goals): residential soil = 23 mg/kg; industrial soil = 350 mg/kg; residential air = 0.00031 µg/m^3; industrial air = 0.0014 µg/m^3; tap water = 6 µg/L.

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Recommended exposure limit (REL) (10-h TWA) = 0.05 mg/m^3 for cemented tungsten carbide containing > 2% Co (as Co); = 0.05 mg/m^3 for cobalt metal dust and fume (as Co); = 0.1 mg/m^3 for cobalt carbonyl (as Co) and cobalt hydrocarbonyl (as Co).

Immediately dangerous to life and health (IDLH) limit = 20 mg/m^3 for cobalt metal dust and fume (as Co).

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Cobalt–Tungsten Carbide: Powders and Hard Metals

CAS No.: none assigned

Reasonably anticipated to be a human carcinogen

First listed in the *Twelfth Report on Carcinogens* (2011)

Also known as Co/WC, WC/Co

Carcinogenicity

Cobalt–tungsten carbide powders and hard metals are *reasonably anticipated to be human carcinogens* based on limited evidence of carcinogenicity from studies in humans and supporting evidence from studies on mechanisms of carcinogenesis.

Cancer Studies in Humans

Epidemiological studies provide evidence for the carcinogenicity of cobalt–tungsten carbide powders and hard metals based on (1) consistent findings of excess lung-cancer mortality among cobalt–tungsten carbide hard-metal manufacturing workers across studies, (2) higher risks among individuals with higher exposure levels, and (3) positive exposure-response relationships that cannot be explained by confounding with tobacco smoking. However, the epidemiological data are limited, because there are few studies of independent populations.

The published epidemiological literature consists of mortality studies of two independent multi-plant cohorts of cobalt–tungsten carbide hard-metal manufacturing workers, one in France (Moulin *et al.* 1998) and one in Sweden (Hogstedt and Alexandersson 1990), and cohort studies of two individual factories included in the French multi-plant cohort (Lasfargues *et al.* 1994, Wild *et al.* 2000). The French multi-plant cohort included all 10 cobalt–tungsten carbide manufacturing plants in France; in addition, a nested case-control study of lung cancer was conducted within this cohort. The nested case-control study is most informative for evaluating cancer risk, because it used a semi-quantitative exposure scale to evaluate exposure-response relationships and considered potential confounding by exposure to tobacco smoking and other known or suspected occupational carcinogens. The cohort study of the largest French factory shares these advantages; however, because the workers were included in the multi-plant study, it does not provide independent evidence for carcinogenicity. In these two studies, four metrics of exposure were evaluated: (1) exposure level, which was the highest exposure score experienced during an individual's work history (on a scale of 0 to 9), (2) duration of exposure at a level of 2 or higher, (3) unweighted cumulative dose, which assigned the same level to occasional and full-time exposure, thus favoring peak exposure, and (4) frequency-weighted cumulative dose, which weighted exposure level by the frequency of exposure, thus reducing the effect of occasional exposure. The Swedish study, although limited in size, provides supporting information for an independent population.

Excess lung-cancer mortality (of approximately 30%) was found in both multi-plant cohort studies (Hogstedt and Alexandersson 1990, Moulin *et al.* 1998); risk estimates were significantly higher among individuals with higher measures of exposure or longer time since first exposure (latency). In the nested case-control study (Moulin *et al.* 1998), lung cancer risk was significantly higher (odds ratio [OR] = 1.93, 95% CI = 1.03 to 3.62, 35 exposed cases) among workers exposed to cobalt–tungsten carbide (exposure level ≥ 2) than among workers with little or no exposure (exposure level < 2). In exposure-response analyses using workers in the lowest exposure category as the comparison group, lung-cancer risk was significantly higher (by up to fourfold) for workers in the highest categories of both measures of cumulative dose, and an elevated risk of borderline statistical significance was found for workers in the highest exposure-level category. Positive exposure-response relationships were observed for all four measures of exposure: duration (P_{trend} = 0.03), unweighted cumulative dose (P_{trend} = 0.01), frequency-weighted cumulative dose (P_{trend} = 0.08), and exposure level (P_{trend} = 0.08). Adjustment for tobacco smoking or exposure to known or suspected carcinogens did not change the results. The Swedish study had limited ability to evaluate exposure-response relationships because of small numbers of exposed workers with lung cancer. Nevertheless, the risk of lung cancer mortality was significantly increased for workers with exposure duration of over 10 years and latency of over 20 years (standardized mortality ratio [SMR] = 2.78, 95% CI = 1.11 to 5.72, 7 exposed cases). Analyses restricted to workers with at least 10 years' exposure or at least 20 years' latency found somewhat higher SMRs for "high-exposed" than "low-exposed" workers (Hogstedt and Alexandersson 1990).

Excess risks of lung-cancer mortality were also found in studies of the two individual French factories. Wild *et al.* (2000) reported significantly elevated SMRs (by approximately twofold) for lung cancer among all male workers and among male workers ever employed in presintering workshops or with exposure levels of at least 2. The highest SMRs were observed for male workers in the highest exposure categories of all four exposure metrics (level, duration, and both measures of cumulative dose), although the trends were not statistically significant, and the risk estimates were imprecise. In the study by Lasfargues *et al.* (1994), the entire cohort had a significantly increased risk of lung cancer, and the risk was highest among workers in the highest exposure-level category. Although small, this study provides supporting evidence that the findings for the French industry-wide cohort were not due solely to the results for the large factory studied by Wild *et al.*

Both the French multi-plant cohort study (Moulin *et al.* 1988) and the larger study of an individual French factory (Wild *et al.* 2000) found higher risks of lung cancer for exposure to cobalt–tungsten carbide before sintering than after sintering (see Production). The authors stated that exposure was highest during presintering processes; however, there is no evidence of toxicological differences between presintered and sintered materials, and both materials release similar amounts of cobalt ions (see Studies on Mechanisms of Carcinogenesis).

It is unlikely that the excess risks of lung cancer found in the French studies were due to confounding by tobacco smoking or co-exposure to other known carcinogens. In the multi-plant study, the smoking-adjusted odds ratio for cobalt–tungsten carbide exposure (OR = 2.6, 95% CI = 1.16 to 5.82) was similar to the unadjusted risk (OR = 2.29, 95% CI = 1.08 to 4.88). Neither study found increased risks of smoking-related diseases, such as chronic bronchitis and emphysema, and adjustment for smoking or exposure to other occupational carcinogens did not change the findings in the exposure-response analyses (Moulin *et al.* 1988, Wild *et al.* 2000). Neither the Swedish multi-plant study (Hogstedt and Alexandersson 1990) nor the small French cohort study (Lasfargues *et al.* 1994) adjusted for smoking; however, surveys of smoking habits among a subset of workers found smoking rates similar to those in the general population. Overall, the studies are limited by the lack of quantitative exposure assessment and potential confounding; however, exposure misclassification would most likely reduce the likelihood of detecting a true effect.

Studies on Mechanisms of Carcinogenesis

The findings from epidemiological studies are supported by studies on mechanisms of carcinogenesis. Although the mechanism(s) by which cobalt–tungsten carbide causes cancer have not been fully elucidated, it has been shown that (1) cobalt–tungsten carbide releases cobalt ions, (2) cobalt ions affect biochemical pathways related to carcinogenicity, (3) cobalt compounds are carcinogenic in experimental animals, (4) cobalt–tungsten carbide increases the production of reactive oxygen species (ROS) and causes greater cytotoxic, toxic, and genotoxic effects than does cobalt alone, (5) cobalt–tungsten carbide causes key events related to carcinogenesis, including genotoxicity, cytotoxicity, inflammation, and apoptosis (programmed cell death), and (6) the oxidative stress response resulting from increased ROS production may play a role in these key events and may also interfere with cells' ability to repair damage caused by cobalt–tungsten carbide. The combination of the effects from cobalt ions and the oxidative stress response from ROS production provide plausible modes of action for the carcinogenicity of cobalt–tungsten carbide.

Studies in biological fluids, *in vitro* systems, experimental animals, and humans have demonstrated that cobalt is rapidly solubilized from cobalt–tungsten carbide. Cobalt dissolution rates were similar for presintered and sintered cobalt–tungsten carbide incubated in various artificial biological fluids (Stopford *et al.* 2003). Tungsten is not rapidly solubilized from cobalt–tungsten carbide, but can be phagocytized by macrophages (Lombaert *et al.* 2004). Cobalt was also released from hard-metal dust incubated with plasma and lung tissue (Edel *et al.* 1990). In experimental animals administered cobalt–tungsten carbide by intratracheal administration, cobalt was solubilized rapidly, cleared from the lung, distributed in the body, and excreted in the urine (Lison 1996). Rats exposed intratracheally to cobalt–tungsten carbide had more cobalt in the urine than did rats administered cobalt alone, suggesting that tungsten carbide increases the bioavailability of cobalt (Lasfargues *et al.* 1992). Several biomonitoring studies detected elevated levels of cobalt in the urine, lungs, and other tissues of workers exposed to cobalt–tungsten carbide hard metals (Rizzato *et al.* 1986, Nicolaou *et al.* 1987, Gallorini *et al.* 1994, Sabbioni *et al.* 1994b, Scansetti *et al.* 1994, 1998, Linnainmaa and Kiilunen 1997, Goldoni *et al.* 2004).

Soluble cobalt compounds are genotoxic and carcinogenic in experimental animals. Cobalt and cobalt compounds that release cobalt ions *in vivo* are listed as *reasonably anticipated to be human carcinogens* in the Report on Carcinogens based on sufficient evidence of carcinogenicity from studies of cobalt metal, cobalt sulfate, cobalt chloride, and cobalt oxide in experimental animals and supporting evidence from studies on mechanisms of carcinogenesis. Cobalt ions produce ROS, which cause oxidative DNA damage and act on a number of cancer-related molecular targets. Cobalt ions disrupt cell-signaling pathways (Murata *et al.* 1999), inhibit DNA repair (Hartwig 2000, Hartwig *et al.* 2002), regulate genes involved in the response to hypoxia (Beyersmann 2002), replace or mimic essential divalent metal ions, thus altering cellular reactions (Nackerdien *et al.* 1991, Beyersmann and Hartwig 1992, Kawanishi *et al.* 1994, Lloyd *et al.* 1998), and interfere with mechanisms involved in cell-cycle control and modulation of apoptosis (DeBoeck *et al.* 2003b,c).

Numerous *in vitro* studies (reviewed in NTP 2009) and *in vivo* studies (Huaux *et al.* 1995, Lasfargues *et al.* 1995) have shown greater cytotoxic effects (measured primarily by lactate dehydrogenase release) for cobalt–tungsten carbide than for either cobalt powder or tungsten carbide alone. The mixture's greater *in vitro* toxicity to macrophages is not fully explained by greater bioavailability of cobalt (Lison and Lauwerys 1992, 1994). Respirable samples collected at various stages of the hard-metal manufacturing process (including powders for pressing, presintered materials, and powders from grinding of sintered materials) caused cytotoxicity and pathological changes in the lungs of rats after intratracheal injection (Adamis *et al.* 1997). In addition, cobalt–tungsten carbide causes a type of respiratory toxicity ("hard-metal disease") that is not observed with exposure to cobalt alone. Hard-metal disease is characterized by a giant-cell interstitial pneumonia that can develop into lung fibrosis (Lison 1996, Lison *et al.* 1996).

There is some evidence that the greater toxicity of cobalt–tungsten carbide may result from a physicochemical reaction that takes place at the interface between certain carbides and cobalt particles (Lison and Lauwerys 1992). The structural features of the two particles may help to explain the effects. Cobalt metal can reduce ambient oxygen, but only at a low rate of reaction, because of the particles' surface characteristics. Tungsten carbide is inert and does not react with oxygen but is a good electron conductor. When cobalt and tungsten carbide particles are associated, the cobalt electrons are transferred to the carbide surface, allowing increased oxygen reduction and thus increased production of ROS. Biochemical studies on the production of ROS have shown that cobalt's capacity to generate hydroxyl radicals is greatly increased by association with tungsten carbide. Formation of the ROS results directly from the interaction of cobalt with tungsten carbide or indirectly from the cobalt ions generated from the Fenton-like reaction of the cobalt metal with the carbide (Lison and Lauwerys 1993, Lison *et al.* 1995). In oxygen-radical-generating systems, post-sintered powders sampled from final machining (grinding) of cobalt–tungsten carbide products produced higher levels of ROS than did pre-sintered samples of cobalt and tungsten carbide separately or as mixtures (Stefaniak *et al.* 2010).

Metal-induced generation of ROS in cellular test systems leads to oxidative stress as a result of increased free radicals and insufficient antioxidative defense. Protective mechanisms include cellular antioxidant systems, the stress-protein response, and the involvement of DNA excision and repair enzymes (Kasten *et al.* 1997, Shi *et al.* 2004, Lombaert *et al.* 2008). Fenoglio *et al.* (2008) studied oxidation of the antioxidant glutathione and cysteine sulfhydryl groups by cobalt–tungsten carbide dust–induced ROS and reported dust-concentration-dependent generation of thiyl radicals at particle surface sites. Depletion of cellular antioxidant defenses could further exacerbate cellular oxidative damage caused by ROS generated by cobalt–tungsten carbide particles.

Regulation of gene expression, including apoptotic, stress-protein, and immune-response pathways, also can be affected by ROS. Lombaert *et al.* (2008) evaluated the effects of cobalt–tungsten carbide exposure *in vitro* on patterns of gene expression in human peripheral-blood mononucleated cells and reported statistically significant up-regulation of apoptosis and stress or defense response pathways and down-regulation of immune-response pathways.

Apoptosis has been associated with exposure to a number of known carcinogens (arsenic, cadmium, chromium, nickel, and beryllium) and possible carcinogens (cobalt and lead). Cobalt chloride has been shown to induce apoptosis through formation of ROS in both human alveolar macrophages and a rat pheochromocytoma cell line (PC12); co-administration of antioxidants suppressed ROS production and restored cell viability (Zou *et al.* 2001, Araya *et al.* 2002). Cobalt–tungsten carbide, tungsten carbide, and cobalt ions induced apoptosis in human lymphocytes; the effect of the mixture was significantly greater than that of tungsten carbide or cobalt alone (Lombaert *et al.* 2004).

Cobalt–tungsten carbide is genotoxic *in vitro* and causes mutations in the lungs of rats exposed *in vivo.* Its genotoxicity (clastogenic effects) may be caused by increased ROS production from the interaction between cobalt and tungsten carbide, from ionic cobalt, or from both. In addition, cobalt ions inhibit DNA repair, which may also contribute to cobalt–tungsten carbide's genotoxic effects. Specifically, cobalt–tungsten carbide caused DNA strand breaks in mouse 3T3 fibroblasts and human peripheral-blood lymphocytes (Anard *et al.* 1997) and micronucleus formation in human peripheral-blood lymphocytes (Van Goethem *et al.* 1997, De Boeck *et al.* 2003c). In these studies, cobalt–tungsten carbide was more genotoxic than cobalt alone. In rats exposed by intratracheal instillation, cobalt–tungsten carbide caused DNA damage and micronucleus formation in the lung (type II pneumocytes) (De Boeck *et al.* 2003a). No increase in DNA damage or micronucleus formation was observed in rat peripheral-blood lymphocytes; however, it is unclear whether circulating lymphocytes are a good reporter for monitoring genotoxic effects from inhaled particles. In humans, neither DNA damage nor micronucleus formation was increased in lymphocytes of cobalt–tungsten carbide hard-metal workers, compared with unexposed workers; however, this study was limited by small sample size (De Boeck *et al.* 2000). Multiple regression analyses (Mateuca *et al.* 2005) indicated that both end points were associated with an interaction between tobacco smoking and exposure, and that micronucleus formation was associated with smoking, working in a cobalt–tungsten carbide plant, and having variant forms of genes coding for DNA repair enzymes (X-ray repair cross-complementing group 3 and 8-oxoguanine DNA glycosylase).

In addition, although the pathogenesis of hard-metal disease is not fully understood, it may involve differences in the susceptibility (genetic and/or health-related) of affected individuals to the toxic effects of increased ROS production due to cobalt–tungsten carbide exposure. Further, the mechanisms for fibrosing alveolitis and lung cancer in hard-metal workers may be related, conceivably involving oxidative damage and/or inflammatory events (IARC 2006).

Cancer Studies in Experimental Animals

No studies in experimental animals were identified that evaluated the relationship between cancer and exposure specifically to cobalt–tungsten carbide powders or hard metals.

Properties

This listing includes powders and dusts (either unsintered or sintered) containing both cobalt and tungsten carbide and hard metals containing both cobalt and tungsten carbide. Powders containing both cobalt and tungsten carbide may result from combination of these materials during manufacture of hard metals, and dusts containing both materials may result from production, finishing, or maintenance (e.g., sharpening or grinding) of cobalt–tungsten carbide hard-metal products. Cobalt–tungsten carbide hard metals are composites of tungsten carbide particles (either alone or in combination with smaller amounts of other carbides) with a metallic cobalt powder as a binder, pressed into a compact, solid form at high temperatures by a process known as "sintering." Cobalt–tungsten carbide hard metals are commonly referred to as "cemented carbides" in the United States, but the term "sintered carbide" also may be used, and some sources

refer to cobalt–tungsten carbide products simply as "tungsten carbides" (Brookes 2002).

The physical properties of cobalt–tungsten carbide hard metals vary with the relative proportions of cobalt, tungsten carbide, and other carbides, but they have common properties of extreme hardness, abrasion resistance, and toughness. Tungsten carbide is hard (able to resist cutting, abrasion, penetration, bending, and stretching) but brittle; cobalt is soft but tough (able to withstand great strain without tearing or breaking). The composition of commercial-grade cobalt–tungsten carbide hard metals can vary greatly; it generally ranges from 50% to 97% tungsten carbide (along with other metallic carbides such as titanium carbide or tantalum carbide) and from 3% to 16% cobalt, with variations in grain size and additives. The proportion of cobalt as the binding metal in the composite hard metal depends on the intended use (Azom 2002). Cobalt–tungsten carbide hard metals for various uses have Vickers hardness values (a measure of the resistance of a substance to indentation by a diamond penetrator of special profile) typically ranging from 1250 to 1900 (Brookes 1998).

The crystalline structure of cobalt–tungsten carbide includes the structures individually of cobalt, which can exist as either hexagonal or cubic crystals, and tungsten carbide, which consists primarily of W_2C, WC, and possibly other carbides (Upadhyaya 1998b). The phase diagram for the combination of cobalt and tungsten carbide is extremely complex, as tungsten can form a solid solution in cobalt, and cobalt can form carbides with carbon; the overall relationship varies with the concentrations of the major components and the temperature.

Mixtures of cobalt and tungsten carbide are more active than the individual components in adsorption of water vapor (with respect to both the amount adsorbed and the interaction energy) and in the catalytic decomposition of hydrogen peroxide (Zanetti and Fubini 1997). Physical and chemical properties of tungsten carbide and cobalt are listed in the following table.

Property	Cobalt	Tungsten carbide
Molecular or atomic weight	58.9	195.9
Density	8.92	15.6
Melting point	1,495°C	2,785°C
Boiling point	2,927°C	6,000°C
Vapor pressure	1 Pa at 1,517°C (0.0075 mmHg)	NR

Source: HSDB 2010. NR = not reported.

Use

About 70% of cobalt–tungsten carbide hard-metal production is used for cutting tools and 30% for wear-resistant materials, primarily for tools for mining and grinding operations (Santhanam 2003). Hard-metal grades for machining are assigned International Organization for Standardization (ISO) codes beginning with "P" for machining of steel, "M" for multiple purposes, including machining of steel, nickel-based superalloys, and higher-tensile-strength (ductile) cast iron, and "K" for cutting of lower-tensile strength (gray) cast iron, nonferrous metals, and nonmetallic materials.

Production

Cobalt–tungsten carbide hard metals were developed in Germany during and after World War I and marketed commercially by a German company in 1927 as Widia, which consisted of tungsten carbide with 6% cobalt as binder (Brookes 1998, Upadhyaya 1998a). Cobalt–tungsten carbide hard-metal manufacturing processes vary somewhat, but all involve production of cobalt and tungsten carbide powders, which are mixed, pressed into a compact, solid form, and sintered by heating to about 1,500°C. The manufacturing process consists of three steps: Step 1, producing the cobalt and tungsten carbide powders; Step 2, mixing, drying, pressing, presintering, shaping the presintered hard metal, and sintering; and Step 3, finishing the sintered products, which includes grinding and sharpening.

Worldwide use of cemented carbides has increased steadily over the years, from about 10 tons in 1930 to 30,000 tons per year in the early 2000s (Azom 2002). In 2004, estimated U.S. production of hard-metal products totaled 5,527 metric tons (6,080 tons) (Hsu 2004). The U.S. Geological Survey (USGS 2008a,b) estimated that 792 metric tons (873 tons) of cobalt (9.3% of total U.S. cobalt consumption) and 6,610 metric tons (7,286 tons) of tungsten (56% of total U.S. tungsten consumption) was used in the production of cemented carbides in the United States in 2007. In 2008, 127 U.S. and Canadian companies were identified that produced or supplied cobalt–tungsten carbide and materials made from cobalt–tungsten carbide (ThomasNet 2008), and the Cemented Carbide Producers Association had 22 U.S. members and partner members (CCPA 2008). In 2017, the United States imported about 7.5 million pounds and exported about 4.4 million pounds of tungsten carbide (USITC 2018); no data specific for U.S. imports or exports of cobalt-tungsten carbide were found

Exposure

The major source of exposure to cobalt–tungsten carbide powders and hard metals is occupational. However, people who live in the vicinity of hard-metal production or maintenance facilities could be exposed to cobalt–tungsten carbide hard-metal dusts. Although no exposure levels for the general population were found, some studies provided data on possible environmental contamination from the manufacture or maintenance of hard-metal products. Soil sampled from the rear of a cemented carbide tool-grinding plant contained cobalt at concentrations of up to 12,780 mg/kg (Abraham and Hunt 1995). The concentrations of tungsten and cobalt in airborne particulates in Fallon, Nevada, and four nearby towns were characterized by Sheppard *et al.* (2006), who found higher levels of tungsten (0.1 to 40.9 ng/m^3) and cobalt (0.02 to 0.16 ng/m^3) in Fallon than in the other towns. The authors suggested that a hard-metal facility located in Fallon could be a candidate source for airborne exposure to the metals, a suggestion that has been disputed (see NTP 2009).

Sources of occupational exposure to cobalt–tungsten carbide during the manufacture of hard metals include the processes of mixing, drying, pressing, presintering, shaping, and sintering (parts of Step 2, as described under Production) and the processes of grinding and sharpening sintered products (parts of Step 3, as described under Production). Exposure to cobalt–tungsten carbide hard metals can also occur from other miscellaneous manufacturing operations, during processing of hard-metal scrap for recycling, and during end use and maintenance of hard-metal tools. Particle size (and hence respirable fraction), morphology, and concentrations of airborne dusts and bulk dusts were found to differ among production areas (Stefaniak *et al.* 2007). For cobalt-containing particles, the minimum mass median aerodynamic diameter (MMAD) was 6 µm (for dry grinding), and the maximum MMAD was over 18 µm (for scrap reclamation and pressing operations); the MMAD for powder mixing was around 10 µm, which is generally considered the maximum diameter for respirable particles in humans. Inhalable, thoracic, and respirable particles were found in all work areas of three facilities that together carried out the cobalt–tungsten carbide manufacturing process, with the highest levels reported for the powder-mixing area (Stefaniak *et al.* 2009). Cobalt and tungsten have been detected in workers' urine, blood, hair, toenails, and bronchoalveolar lavage fluid, and through open lung and transbronchial biopsy (NTP 2009).

Step 2 processes, particularly powder-processing operations, generally are associated with the highest airborne exposures; several studies reported cobalt concentrations approaching or exceeding 5,000 µg/m^3 (NTP 2009). A maximum mean cobalt air concentration of 32,740 µg/m^3 (range = 44 to 438,000 µg/m^3) was reported during weighing and mixing operations in a U.S. manufacturing facility (Sprince *et al*. 1984). An Italian study reported a mean tungsten air concentration of 26 µg/m^3 (Sabbioni *et al*. 1994a), and a German study reported a maximum single measurement of 254 µg/m^3 (Kraus *et al*. 2001). Among workers involved in Step 2 manufacturing processes, cobalt was detected in the urine (at up to 2,100 µg/L), blood or serum (at up to 32 µg/L), and hair (at up to 25.8 ppm), and tungsten was detected in urine (at up to 169 µg/L).

Cobalt air concentrations reported for Step 3 processes (including tool finishing, grinding, and reconditioning operations) have generally been lower than those for Step 2, but have exceeded 1,000 µg/m^3 in some studies (NTP 2009). For Step 3 processes, a maximum mean cobalt air concentration of 1,292 µg/m^3 and a maximum single measurement of 2,440 µg/m^3 were reported, both for dry-grinding operations. For tungsten in air, a maximum mean concentration of 5,160 µg/m^3 and a maximum single measurement of 12,800 µg/m^3 were reported. Among workers involved specifically in Step 3 processes, cobalt was detected in urine (at up to 730 µg/L), blood (at up to 39 µg/L), and hair (at up to 9.11 ppm). Tungsten also was detected in urine (at up to 1,000 µg/L) and blood (at up to 60 µg/L).

A few studies reported on exposure for jobs outside of the cobalt–tungsten carbide production process. McDermott (1971) reported airborne cobalt concentrations during packing operations (10 to 250 µg/m^3), equipment cleaning (40 to 820 µg/m^3), and miscellaneous operations (10 to 6,700 µg/m^3), but the nature of these operations was not defined further. Maintenance activities (including housekeeping) were reported by Scansetti *et al.* (1985) to result in airborne cobalt concentrations exceeding 50 µg/m^3, and Kraus *et al.* (2001) reported urinary levels associated with maintenance activities ranging from 1.3 to 4.7 µg/L for cobalt and 1.5 to 5.3 µg/L for tungsten.

Information on exposure from the end use of hard-metal tools is limited; however, exposure appears to be minimal. Pellet *et al.* (1984) reported cobalt air concentrations of 180 to 193 µg/m^3 and a mean urinary cobalt concentration of 11.7 µg/L associated with use of hard metal; however, no additional information was provided for these data. No other information was found that directly demonstrated exposure to cobalt–tungsten carbide powders and hard metals by end users of products containing the material. The Washington State Department of Labor, in a Hazard Alert issued in March 1995, stated that there was no evidence of substantial exposure to cobalt during the use of tools containing tungsten carbide or other hard metals (WSDLI 1995).

Several studies found significant correlations between cobalt concentrations in air and in workers' blood or urine (Ichikawa *et al.* 1985, Scansetti *et al.* 1985, Lison *et al.* 1994, Sabbioni *et al.* 1994b). Urinary cobalt levels for hard-metal workers have been reported to increase through the workday (Torra *et al.* 2005) and workweek (Lison *et al*. 1994, Scansetti *et al*. 1998, Torra *et al.* 2005). In one study, urinary cobalt concentrations were significantly higher ($P < 0.005$) at the end of a shift than at the beginning of the shift, with significant increases "day in and day out" during the workweek (Torra *et al.* 2005).

Regulations

U.S. Environmental Protection Agency (EPA)

Clean Water Act

Tungsten and cobalt discharge limits are imposed for numerous processes during the production of tungsten or cobalt at secondary tungsten and cobalt facilities processing tungsten or tungsten carbide scrap raw materials.

Discharge limits for tungsten are imposed for numerous processes during the production of tungsten at primary tungsten facilities.

Discharge limits for cobalt are imposed for numerous processes during the production of cobalt at primary cobalt facilities.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Cobalt and cobalt compounds are listed substances subject to reporting requirements.

Occupational Safety and Health Administration (OSHA, Dept. of Labor)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2018, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limits (PEL) (8-h TWA) = 0.1 mg/m^3 for cobalt metal, dust, and fume (as Co); = 5 mg/m^3 for insoluble tungsten compounds (as W).

Short-term exposure limits (STEL) = 10 mg/m^3 for insoluble tungsten compounds (as W).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.02 mg/m^3 for cobalt and inorganic cobalt compounds; = 5 mg/m^3 for tungsten metal and insoluble compounds.

Threshold limit value – short-term exposure limit (TLV-STEL) = 10 mg/m^3 for tungsten metal and insoluble compounds.

Biological exposure index (BEI) (end of shift at end of workweek) = 15 µg/L for cobalt in urine.

National Institute for Occupational Safety and Health (NIOSH, CDC, HHS)

Recommended exposure limit (REL) (10-h TWA) = 0.05 mg/m^3 for cemented tungsten carbide containing > 2% Co (as Co); = 0.05 mg/m^3 for cobalt metal dust and fume (as Co); = 5 mg/m^3 for tungsten and insoluble tungsten compounds (as W).

Immediately dangerous to life and health (IDLH) limit = 20 mg/m^3 for cobalt metal dust and fume (as Co).

Short-term exposure limit (STEL) = 10 mg/m^3 for tungsten and insoluble tungsten compounds (as W).

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